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OBSERVATIONS ON INDUCED THIAMINE (VITAMIN B_1) DEFICIENCY IN MAN

RAY D. WILLIAMS, M.D.
Fellow in Medicine, the Mayo Foundation

HAROLD L. MASON, PH.D.

RUSSELL M. WILDER, M.D., PH.D.
AND
BENJAMIN F. SMITH, M.D.
ROCHESTER, MINN.

Reports of controlled observations on induced thiamine (vitamin B_1) deficiency in human beings have been few,[1] and in only two of these reports [1c,d] has the restriction of vitamins been limited to thiamine. One of these studies [1d] was reported by three of us (Williams, Mason and Smith) in December 1939. In that study, 4 young women for twenty-one weeks received a diet which was more deficient in vitamin B_1 than commonly is reported in association with the syndrome of beriberi. This diet was made adequate in vitamin A, ascorbic acid,

From the Rochester State Hospital and the Mayo Foundation.

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From the Division of Biochemistry (Dr. Mason), the Mayo Clinic, and from the Departments of Medicine (Dr. Wilder) and of Neurology and Psychiatry (Dr. Smith), the Mayo Foundation.

1. (*a*) Cowgill, G. R.: Human Requirements for Vitamin B_1, in The Vitamins: A Symposium Arranged Under the Auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association, Chicago, American Medical Association, 1939, chap. 12, pp. 229-248. (*b*) Elsom, K. O.: Experimental Study of Clinical Vitamin B Deficiency, J. Clin. Investigation **14**: 40-51 (Jan.) 1935. (*c*) Jolliffe, N.; Goodhart, R.; Gennis, J., and Cline, J. K.: The Experimental Production of Vitamin B_1 Deficiency in Normal Subjects: The Dependence of the Urinary Excretion of Thiamin on the Dietary Intake of Vitamin B_1, Am. J. M. Sc. **198**:198-211 (Aug.) 1939. (*d*) Williams, R. D.; Mason, H. L., and Smith, B. F.: Induced Vitamin B_1 Deficiency in Human Subjects, Proc. Staff Meet., Mayo Clin. **14**:787-793 (Dec. 13) 1939. (*e*) Elsom, K. O.; Lukens, F. D. W.; Montgomery, E. H., and Jonas, L.: Metabolic Disturbances in Experimental Human Vitamin B Deficiency, J. Clin. Investigation **19**:153-161 (Jan.) 1940.

proteins and minerals and in addition was supplemented with crystalline preparations of riboflavin and nicotinic acid. The delayed development of symptoms and failure of the subjects to show the classic signs of beriberi prompted repetition of the study with other subjects. Also it seemed desirable to provide more adequately for the factors of the vitamin B complex other than thiamine. For this purpose autoclaved yeast was given instead of crystalline riboflavin and nicotinic acid.

PROCEDURE

Six white women, patients of the Rochester State Hospital, were chosen on the basis of their voluntary cooperation, absence of physical defects,[2] absence of any history of abnormal nutrition and quiescence of associated mental illness. These women were active physically and were engaged in hospital housework. The group included asthenic and sthenic, hyperkinetic and sedentary, thin and well nourished women. Their ages ranged from 21 to 46 years and their weights from 50 to 65 Kg.

A basal diet was arranged to provide not more than 150 micrograms (0.15 mg.) of thiamine (that is, 50 international units of vitamin B_1) daily. The diet was composed of white flour, sugar, tapioca, corn starch, washed polished rice, white raisins, egg white, cottage cheese, butter, hydrogenated fat, black tea and cocoa. Many samples of each of these foods were analyzed for their content of thiamine, and in the calculations of intake of thiamine the highest analytic values were used. These analyses were by the method of Hennessy and Cerecedo.[3] The allowance of carbohydrate was never less than 175 Gm., and, in addition, sugar, candies and fat were permitted ad libitum. There was not more than 0.08 microgram of thiamine to each calory in the diet and 0.12 microgram of thiamine to each nonfat calory. The allowance of protein was well above the minimal requirement, although, because many foods rich in protein are carriers of thiamine, the variety of such foods was necessarily limited. The diet was supplemented with 20 Gm. of autoclaved brewers' yeast (containing only 8 micrograms of thiamine), 50 mg. of crystalline ascorbic acid, halibut liver oil in an amount to provide 8,000 units of vitamin A, iron and calcium.

The urine was analyzed for thiamine at intervals not less frequent than once weekly. The analytic method of Hennessy and Cerecedo was used for this purpose. These analyses served as a suggestive index of the degree of thiamine deprivation and provided a check or control for the intake of thiamine. Body weight, physical and neurologic signs and symptoms, tolerance for exercise, electrocardiographic changes, size of the heart as determined by roentgen examination, gastric analysis, dextrose tolerance, blood counts, blood sugar, plasma protein, blood content of bisulfite-binding substances and lactic acid (before and after exercise) and basal metabolic rates were determined at intervals during the period of deprivation of thiamine and again in a subsequent period, when thiamine was administered. Gastrointestinal motility as evidenced by roentgen examination after a barium

2. Except in case 3, in which deformity of the left leg was present owing to anterior poliomyelitis during childhood.

3. Hennessy, D. J., and Cerecedo, L. R.: The Determination of Free and Phosphorylated Thiamin by a Modified Thiochrome Assay, J. Am. Chem. Soc. **61**:179-183 (Jan.) 1939.

sulfate meal was studied at the end of the period of restriction of thiamine and again during the following period, when thiamine was administered.

Needless to say, the carrying out of observations of this nature entailed unusual cooperation of nursing and dietary assistants.[4]

OBSERVATIONS ON SUBJECTS WHILE THEY WERE RECEIVING THE DIET DEFICIENT IN THIAMINE

The period of restricted intake of thiamine extended from Dec 12, 1939 to March 9, 1940 (eighty-eight days). The more conspicuous signs and symptoms observed during the period of inadequate intake of thiamine are presented in table 1. It can be seen that the amount of thiamine excreted in the urine fell rapidly to remarkably low values. The time of onset of signs and symptoms varied. In general, the more active subjects were the first to experience symptoms. The abnormalities ultimately noted in all of the subjects who were deprived of thiamine for periods of several weeks were: depressed mental states, generalized weakness, dizziness, backache, soreness of muscles, palpitation, dyspnea and precordial distress (pseudoangina) on exertion, insomnia, anorexia, nausea, vomiting, loss of weight, atony of muscles, very slight roughness of the skin, faint heart sounds, lowered blood pressure and bradycardia when at rest, with tachycardia and sinus arrhythmia on exertion. In all cases physical activity greatly decreased. Less regularly there were observed states of apathy, reawakening of psychotic trends, difficulty of thought and memory, photophobia, headache, abdominal distention, sensations of cold and heat, burning of the soles of the feet, numbness of the legs, fatigue of the ocular muscles, tenderness of the muscles of the calves and depressed tendon reflexes. Changes in the size of the heart were not detectable in any case. Edema was not apparent in any case. The concentration of plasma proteins remained within normal limits in all cases. The values for serum calcium and serum phosphorus remained normal. Anemia did not develop; cheilosis was not seen, and there was no reddening of the skin or of the tongue.

In all cases the capacity for work, as measured with a calibrated chest weight exercising machine, fell progressively during the period of restricted intake of thiamine (fig. 1). Electrocardiographic abnormalities developed. They consisted of diminution in the amplitude of all complexes and particularly of the T waves of the chest leads. In certain instances the T waves became isoelectric or shallowly inverted (fig. 2). In each case the apex of the heart was located by palpation and fluoroscopic examination, and the position for application of electrodes was made the same in all examinations. The records were taken

4. This work was made possible by the assistance of Miss Phyllis Newman and Miss Margaret Pewters.

TABLE 1.—*Summary of Intake of Food, Intake and Excretion of Thiamine, and More Evident Signs and Symptoms During Period of Restricted Intake of Thiamine*

Case	Sex	Age, Years	Height, Cm.	Period of Diet	Diet					Thiamine in Urine, Micrograms	Body Weight, Kilograms	Symptoms
					Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Thiamine, Micrograms			
1	Female	23	163	Nov. 27 to Dec. 7, 1939	261	65	111	2,303	750	320	54.5	Asymptomatic on preliminary observation
				Dec. 8, 1939 to Jan. 12, 1940	275	56	59	1,855	140	24	54.5	Fatigue; anorexia
				Jan. 13 to Feb. 12, 1940	271	57	60	1,852	145	16	53.7	Nausea; lower blood pressure; apathy; decreased activity
				Feb. 13 to March 8, 1940	217	39	49	1,465	121	23	51.4	Vomiting; low blood pressure; weakness of legs; dizziness; depressed reflexes; bradycardia when at rest; tachycardia on exertion
2	Female	46	164	Nov. 27 to Dec. 7, 1939	260	65	108	2,272	750	98	55.5	Asymptomatic on preliminary observation
				Dec. 8, 1939 to Jan. 12, 1940	247	55	57	1,721	139	17	55.5	Fatigue; anorexia; constipation
				Jan. 13 to Feb. 12, 1940	186	43	53	1,393	119	15	50.0	Weakness; nausea; dizziness; tenderness of calves; bradycardia when at rest; tachycardia on exertion; apathy
				Feb. 13 to March 8, 1940	200	32	37	1,261	95	13	45.6	Extreme weakness; vomiting; inactivity; faint heart sounds; low blood pressure
3	Female	26	159	Nov. 27 to Dec. 12, 1939	274	64	111	2,351	750	68	64.5	Asymptomatic on preliminary observation
				Dec. 13, 1939 to Jan. 12, 1940	284	52	58	1,806	137	10	66.4	Fatigue; anorexia; constipation; mental depression
				Jan. 13 to Feb. 12, 1940	224	44	53	1,549	122	14	64.5	Fatigue; nausea; insomnia; tenderness of calves; mental depression
				Feb. 13 to March 8, 1940	213	38	48	1,436	107	15	62.7	Vomiting; weakness; dizziness; bradycardia when at rest; tachycardia on exertion; mental depression
4	Female	33	155	Nov. 27 to Dec. 12, 1939	274	64	111	2,462	750	124	50.0	Asymptomatic on preliminary observation
				Dec. 13, 1939 to Jan. 12, 1940	322	59	59	2,075	149	12	49.2	Fatigue; anorexia; constipation
				Jan. 13 to Feb. 12, 1940	215	40	48	1,452	113	10	46.5	Weakness; nausea; mental depression; lower blood pressure; faint heart sounds; bradycardia when at rest; tachycardia on exertion
				Feb. 13 to March 8, 1940	176	22	28	1,044	73	14	41.8	Weakness; vomiting; dizziness; tenderness of calves; paresthesia of legs; low blood pressure; bradycardia when at rest; tachycardia on exertion

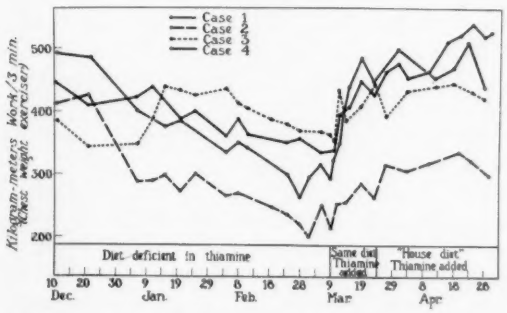

Fig. 1.—Capacity of subjects for work, as measured by a calibrated chest weight exerciser, during the period of restricted intake of thiamine (Dec. 12, 1939 to March 8, 1940) and during the subsequent period in which the restricted diet was supplemented with thiamine hydrochloride (March 9 to 26, 1940).

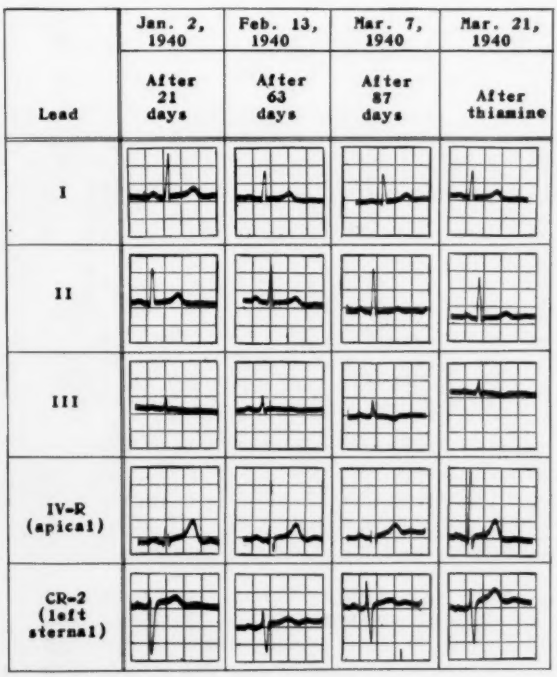

Fig. 2.—Electrocardiographic changes in the period of restriction of thiamine and after thiamine was given.

with the subject in the recumbent position. In 3 of the 4 subjects who received the diet low in thiamine for prolonged periods, blood sugar (method of Miller and Van Slyke [5]) time curves became diabetic in type (fig. 3), and values for the concentration of bisulfite-binding substances in the blood (method of Clift and Cook [6]) and for lactic acid (method of Miller and Muntz [7]) in the blood were elevated irregularly before, but particularly after, exercise (fig. 4). In all cases gastric acidity, as determined by a test meal of 100 cc. of 7 per cent solution of alcohol, was decreased, and gastrointestinal motility as evidenced by roentgen examination after a barium meal was impaired (fig. 5).

The period of restricted intake of thiamine was terminated after eighty-eight days (March 9, 1940) by giving a subcutaneous injection of 1 mg. of thiamine hydrochloride. The diet low in vitamin B_1 was

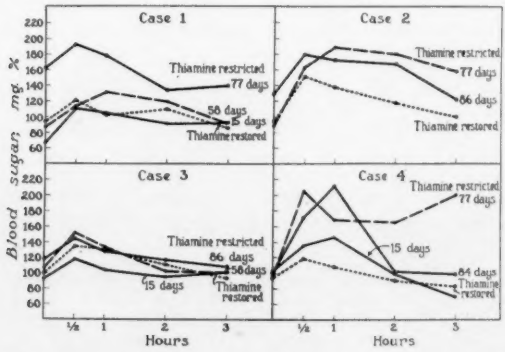

Fig. 3.—Blood sugar time curves during the period of restricted intake of thiamine (Dec. 12, 1939 to March 8, 1940) and again during the period in which the restricted diet was supplemented with thiamine hydrochloride (March 9 to 26, 1940).

continued until March 26. During the interval from March 9 to March 15 daily injections of small doses of thiamine hydrochloride were made, and the amount of thiamine contained in the urine was determined daily.

Subjective improvement was observable in every case within a few hours after the initial injection of 1 mg. of thiamine hydrochloride. Nausea and vomiting ceased; food which previously had been revolting

5. Miller, B. F., and Van Slyke, D. D.: A Direct Microtitration Method for Blood Sugar, J. Biol. Chem. **114**:583-595 (July) 1936.

6. Clift, F. P., and Cook, R. P.: A Method for Determination of Some Biologically Important Aldehydes and Ketones, with Special Reference to Pyruvic Acid and Methylglyoxal, Biochem. J. **26**:1788-1799, 1932.

7. Miller, B. F., and Muntz, J. A.: A Method for the Estimation of Ultramicroquantities of Lactic Acid, J. Biol. Chem. **126**:413-421 (Nov.) 1938.

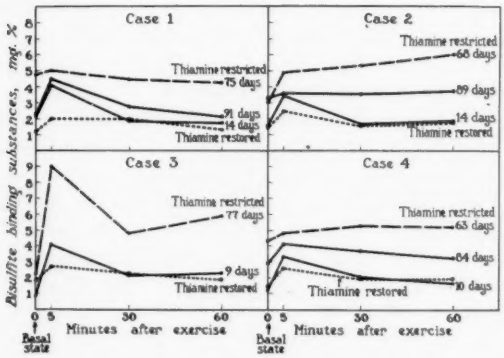

Fig. 4.—Values of bisulfite-binding substances in the blood under basal conditions and at intervals after one minute of vigorous exercise, during the period of restricted intake of thiamine (Dec. 12, 1939 to March 8, 1940) and again during the period in which the restricted diet was supplemented with thiamine hydrochloride (March 9 to 26, 1940).

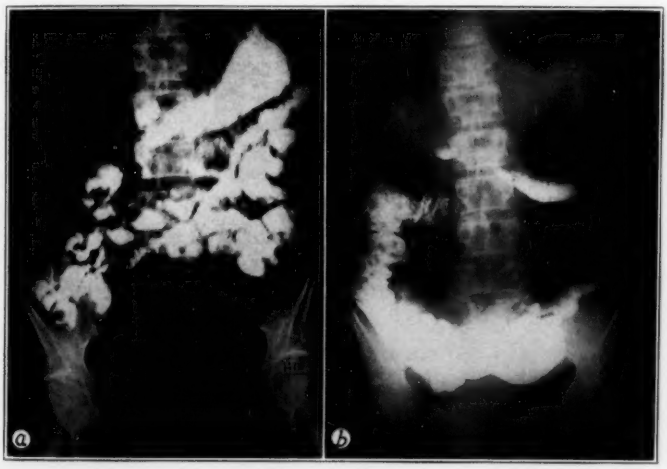

Fig. 5.—Roentgen evidence of impaired gastrointestinal motility (case 4) three hours after plain barium sulfate meals. Roentgenogram *a* was made March 8, 1940, after a period of restriction of intake of vitamin B_1 (Dec. 12, 1939 to March 8, 1940); roentgenogram *b* was made March 22, 1940, in a period (March 9 to 26) in which the patient was receiving a dietary regimen restricted in vitamin B_1 content and supplemented with thiamine hydrochloride.

to the patient was eaten without urging; fatigue disappeared; activity was resumed, and apathy was replaced by lively interest in ward work and current events. During the eighteen days (March 9 to 26 inclusive) in which administration of thiamine hydrochloride represented the only change made, all signs and symptoms incident to the period of restriction of thiamine disappeared. The electrocardiograms became normal; the previously diabetic type of sugar tolerance curve was replaced by a normal curve; previously abnormal values for bisulfite-binding substances and lactic acid were replaced by normal values, and the previously sluggish motility of the intestinal tract was replaced by normal activity. In case 1, however, depressed tendon reflexes and weakness of the muscles of the calves persisted in a diminishing degree for several weeks.

OBSERVATIONS ON SUBJECTS DURING ADMINISTRATION OF A DIET DEFICIENT IN THIAMINE, SUPPLEMENTED WITH THIAMINE CHLORIDE

Two of the 6 subjects placed on the diet restricted in thiamine (cases 5 and 6) were given thiamine hydrochloride orally. This was done without their knowledge. The basal diet contained 0.15 mg. of thiamine. The initial dose of thiamine hydrochloride was 0.5 mg. It was given eleven days after starting the diet, at a time when the urinary content of thiamine had fallen to very low levels. Thereafter a daily dose of thiamine hydrochloride was administered in gradually increasing doses up to 2 mg. a day (table 2). A substantial increase of thiamine in the urine did not occur until the intake of the vitamin had reached 0.95 mg. Marked improvement in the clinical state of the subject was accompanied with an increased capacity for work (fig. 6). On March 27, when the daily level of intake was lowered from 2 mg. to 0.75 mg., the capacity for work again fell, and when more thiamine was given, on April 10, the capacity for work again increased.

In both of these subjects an intake of less than 0.95 mg. of thiamine daily was associated with fatigue, irritability, poor appetite, insomnia, soreness of muscles and constipation. On the other hand, a feeling of unusual well-being associated with unusual stamina and enterprise accompanied the period (March 7 to 26) in which the intake of thiamine was at the level of 2 mg. daily. This was followed by a letdown when the intake of thiamine was lowered by substituting the routine hospital diet for the basal diet which had been supplemented with thiamine hydrochloride. The change at this time was so striking that 1 subject begged to be returned to the basal diet. During the period when the subjects were receiving the basal diet supplemented with less than 0.80 mg. of thiamine hydrochloride the electrocardiograms were slightly

abnormal. The abnormality consisted of diminution in the amplitude of the T waves of the left sternal lead (C R-2). The same abnormality was not observable in subsequent tracings (fig. 7). The blood sugar

TABLE 2.—*Data on Subjects Who Received the Thiamine-Deficient Diet, Supplemented with Thiamine Hydrochloride*

Case; Sex	Age; Height, Cm.	Period of Diet	Diet				Thiamine			Body Weight, Kilograms
			Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Food, Micrograms	Solution, Micrograms	Urine Micrograms	
5 Female	42 yr. 152.5	Nov. 27 to Dec. 7, 1939	260	65	111	2,300	750	...	185	51.0
		Dec. 8 to Dec. 17, 1939	297	56	57	1,925	152	...	37	51.5
		Dec. 18, 1939 to Jan. 13, 1940	267	55	58	1,810	140	500	30	53.7
		Jan. 14 to Jan. 23, 1940	286	60	61	1,933	150	600	36	52.4
		Jan. 24 to Feb. 5, 1940	277	56	59	1,863	143	700	57	52.8
		Feb. 6 to Feb. 15, 1940	313	62	62	2,058	158	800	90	52.8
		Feb. 16 to Feb. 20, 1940	275	58	60	1,872	155	900	120	52.4
		Feb. 21 to March 7, 1940	267	52	59	1,807	135	1,000	212	52.0
		March 8 to March 26, 1940	274	53	59	1,839	146	2,000	562	52.8
		March 27 to April 9, 1940	260	65	111	2,300	750	...	132	54.3
6 Female	28 yr. 154	Nov. 27 to Dec. 7, 1939	254	64	108	2,244	708	...	117	51.0
		Dec. 8 to Dec. 17, 1939	273	54	58	1,830	134	...	20	50.1
		Dec. 18, 1939 to Jan. 13, 1940	242	56	60	1,732	142	500	28	51.0
		Jan. 14 to Jan. 23, 1940	313	64	61	2,057	156	600	30	49.7
		Jan. 24 to Feb. 5, 1940	297	58	59	1,951	150	700	60	49.6
		Feb. 6 to Feb. 15, 1940	267	53	57	1,793	144	800	64	48.5
		Feb. 16 to Feb. 20, 1940	234	47	55	1,619	126	900	83	49.2
		Feb. 21 to March 7, 1940	280	54	58	1,894	141	1,000	97	48.3
		March 8 to March 26, 1940	258	48	58	1,746	132	2,000	507	48.3
		March 27 to April 9, 1940	232	60	108	2,140	684	...	60	49.7

time curves and the curves for the concentration of bisulfite-binding substances and of lactic acid after exercise showed no unusual features in these cases.

In case 5 a minimal degree of papilledema was noted at a time when the intake of thiamine was restricted. It disappeared later, when the intake of thiamine had been increased to 0.85 mg. daily. This recalls

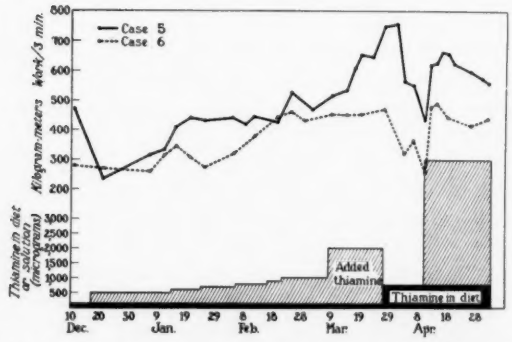
Case 5
Case 6
Kilogram-meters work/3 min.
Thiamine in diet (milligrams)
Added thiamine
Thiamine in diet
10 20 30 9 19 29 8 18 28 9 19 29 8 18 28
Dec. Jan. Feb. Mar. Apr.

Fig. 6.—Capacity for work, as measured by a calibrated chest weight exerciser, of subjects receiving the thiamine-deficient diet, supplemented with varying amounts of thiamine hydrochloride.

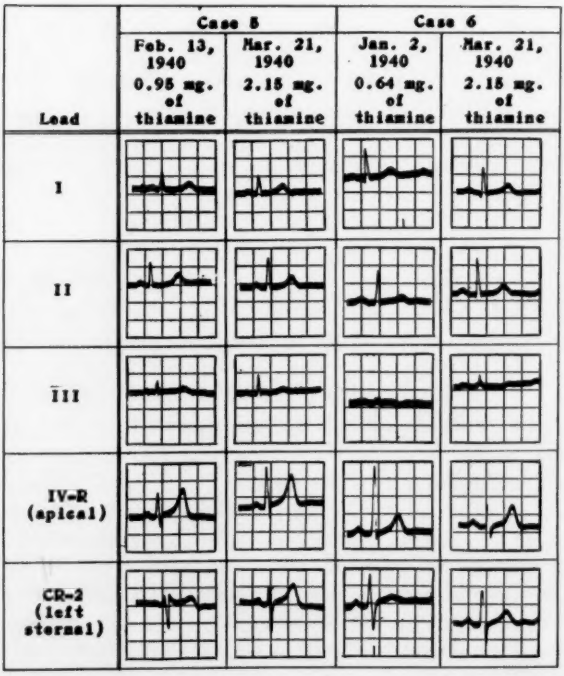

Fig. 7.—Electrocardiographic changes in the period in which the thiamine-deficient diet was supplemented with thiamine hydrochloride.

the observation of papilledema in cases of neuritis axialis reported by Kagawa.[8] An instance of papilledema in a patient with pellagra and associated evidence of thiamine deficiency was called to the attention of one of us (Wilder) during a recent visit to the nutrition clinic of the Hillman Hospital in Birmingham, Ala.

COMMENT

Observations previously reported by three of us (Williams, Mason and Smith) are confirmed by the results of the work described here, in which 6 subjects for eighty-eight days received a diet which provided daily less than 0.15 mg. of thiamine (50 international units of vitamin B_1) but which otherwise was adequate nutritionally. After eleven days 2 of these subjects were given thiamine hydrochloride orally, without their knowledge, in gradually increasing daily doses. The 4 subjects who obtained no supplementary thiamine experienced striking evidences of nutritional deficiency. The 2 subjects whose diets were supplemented with thiamine also revealed evidences of deficiency until their total intake of the vitamin reached 0.95 mg. daily. From then on they were free from symptoms and performed as effectively on a chest weight exercise machine as at the start of the observations. This provided a control of the adequacy of the basal diet in factors other than thiamine. However, with further increases in the allowance of thiamine they improved still more, and when the intake reached 2 mg. a day they were strikingly more alert and attentive, and their performance with the chest weight exercise was much more satisfactory than it had been originally (fig. 6). At the end, when the intake of thiamine was lowered by a return to the routine hospital diet, well-being, alertness and work performance fell again to what they had been originally. This constitutes strong evidence that the institutional diet, which by calculation contained approximately 0.6 to 0.8 mg. of thiamine daily, provided less than an optimal allowance of thiamine. The food in this hospital compares favorably, in our opinion, with that in most institutions. Therefore, the observations indicate that institutional diets in general may be subject to criticism on the score of providing less thiamine than is desirable.

Another conclusion suggested by our observations is that the isolated withdrawal of thiamine from the diet does not produce beriberi. In the earlier study [1d] 4 subjects were given food that contained less than 0.155 mg. of thiamine per day for one hundred and forty-seven days, and in the study which we now are reporting 4 other subjects received a diet that provided less than 0.15 mg. for eighty-eight days. Yet in

8. Kagawa, S.: Studies on the Relation of Neuritis Axialis to Beriberi in Japan, Jap. J. M. Sc., VIII, Int. Med., Pediat. & Psychiat. **5**:1-60 (Dec.) 1938.

both studies, edema, which is said to develop in at least one third of all cases of beriberi, cardiac dilatation, which is a common occurrence with beriberi, and neuritic pain, which is regarded as a conspicuous feature of beriberi, were absent. Tenderness of the muscles of the calves, which in no case was severe, paresthesia of the feet and legs, which never was more than mild, and diminution of tendon reflexes were observed, although not with any regularity, and pain was not present in any degree. Thus we are led to question whether thiamine is the vitamin the lack of which is responsible for the classic features of beriberi and to suggest that deficiency of factors of the vitamin B complex other than thiamine may be more important in the production of such features than thiamine itself.

We nevertheless are impressed by the degree of debility induced by the isolated withdrawal of thiamine. Fatigue, lassitude and loss of interest in food developed early and increased progressively as the period of deficiency extended, to the point of intolerance for food. So great was this intolerance that uncontrollable vomiting, even after tube feeding and parenteral injection of solutions of sodium chloride and dextrose, automatically brought the observations to a close. The time of development of symptoms and the time of development of severe symptoms differed among the subjects and seemed to be related to physical activity. The subjects who were more active showed symptoms earlier and were more seriously affected later than others who from the beginning were less energetic. In part, also, a seasonal influence may have been manifest. The period of restriction of thiamine in the earlier study began April 4, 1939, and was continued until August 30 (one hundred and forty-seven days) before the severity of anorexia and vomiting necessitated its termination. In the study reported here the period of restriction of thiamine began Dec. 12, 1939 and was continued only until March 9, 1940 (eighty-eight days) before vomiting became equally disturbing. Furthermore, none of the 4 subjects of the earlier study revealed any clear evidence of deficiency until after four or five weeks of restricted intake of thiamine, whereas all 6 subjects of the present study experienced symptoms within ten to fourteen days. The difference was striking. It suggests that a greater total metabolism provoked by low temperature or changeableness of the weather led to a relatively greater requirement for thiamine in the period of the second study.

The disease induced by the isolated restriction of thiamine resembles minutely that disorder which the discriminating psychiatrist designates as neurasthenia. It differs from hysteria, obsessive and compulsive states, anxiety neurosis and other conditions which an undiscriminating physician commonly would lump together with neurasthenia under such designations as chronic nervous exhaustion or functional neurosis. Thus,

neurasthenia, properly defined, may be less of a functional abnormality than has been supposed, and it may depend on improper nutrition of the neurons.

The force of this suggestion can be appreciated best by comparing the symptoms and objective evidences of abnormality which we encountered in our studies with the symptoms and abnormalities associated with neurasthenia as recorded by Wilson.[9] The following paragraphs are quoted from him. The italics have been employed by us to indicate the symptoms which we encountered in cases of induced deficiency of thiamine.

General Symptoms.—Fatigue, often present on slight exertion and may be curiously selective, in that it is chiefly manifested when the patient's interest is at a low ebb. *Loss of weight,* usually dependent on appetite failure.

Local Symptoms.—Alimentary: Capricious appetite, anorexia, indigestion, distension, eructation, nausea, vomiting, constipation or diarrhea, mucous colitis. *Circulatory:* Varying degrees of cardiac discomfort, *tachycardia, palpitation, pseudoanginal sensations, heart irregularity. Vasomotor: Pallor,* blushing, sweating, *coldness, heat* and numerous other phenomena. *Genito-urinary:* Impotence, nocturnal emissions, genito-urinary paresthesias, *dysmenorrhea,* dyspareunia, *frequency of micturition,* increased urinary output, "loose kidneys." *Respiratory system: Frequent "colds," shortness of breath,* sometimes hastened respiratory rate with shallow breathing. *Nervous system: Peculiar sensations in head* and in fact in every portion of the body; feelings of swelling of the scalp, *band around head,* bursting and stuffiness of head, *headache, especially in occipital region,* peculiar, *uncomfortable* or painful *sensations in the abdomen, rectum* or breasts. An almost universal complaint is *backache. Giddiness and dizziness* are common and *insomnia* is rarely absent. There may be *photophobia,* muscae volitantes, and *eye muscle fatigue,* ear noises, intolerance of ordinary sounds. *Mental symptoms: Inability to concentrate, uncertain memory, fear of insanity, awkwardness* and *self-consciousness* in the presence of others, feelings of inferiority, *irritability, depression,* phobias, anxieties.

Not every symptom of neurasthenia was represented in every one of our subjects, but neither is this true of all patients who have neurasthenia. We observed tachycardia only when the patient exerted herself. When she was at rest the pulse was slower than normal; this also is common in cases of neurasthenia. Achlorhydria or hypochlorhydria, which was constant in our subjects in the period when thiamine was restricted, is likewise a frequent accompaniment of neurasthenia. Constipation became the rule in our subjects; diarrhea was infrequent or transient. Possibly long-continued use of cathartics accounts for the diarrhea and the "mucous colitis" that are frequently encountered among patients who have neurasthenia. An explanation for the constipation was

9. Wilson, G.: Neurasthenia, in Musser, J. H.: Internal Medicine: Its Theory and Practice in Contributions by American Authors, ed. 3, Philadelphia, Lea & Febiger, 1938, p. 1235.

found in the slow emptying of the stomach and the sluggish motility of the intestine. These were observed roentgenologically after a barium sulfate meal during the period of deficient intake of thiamine but not after administration of thiamine hydrochloride. The roentgenologist commonly lays little stress on delayed passage of barium through a bowel which otherwise reveals no abnormalities, and we are led to suspect that he thereby may be overlooking cases of thiamine deficiency. Similarly, the cardiologist commonly disregards electrocardiograms that show only diminished amplitude of T waves, yet with our subjects this abnormality first appeared when they were deprived of thiamine; it remained week after week during the period of restriction and was rapidly corrected afterward, when thiamine hydrochloride was administered (fig. 2).

At the end of the period of deprivation of thiamine, the clinical picture presented in all our cases was that of anorexia nervosa, and this condition as one encounters it clinically is usually an end stage of more severe neurasthenia. We wish to make clear, however, that we are comparing the state of thiamine deficiency not with the functional neuroses in general but with neurasthenia (when the term "neurasthenia," is used with the discrimination that we have demanded). Nor do we mean to imply that all patients with conditions diagnosed as neurasthenia could be shown to be victims of thiamine deficiency, especially of a primary deficiency of this vitamin. Possibly only a small percentage of such conditions are nutritional in origin, but it may be that the number is large. What we do suggest, on the basis of observations of the disease induced by withdrawal of thiamine, is that thiamine deficiency, as it exists in this part of the United States, where one observes only a few cases of beriberi or pellagra, should be looked for principally in that large group of patients who have the infirmity to which the diagnosis neurasthenia has appropriately been applied.

McLester [10] has called attention to the similarity of the so-called prepellagrous state and neurasthenia. He wrote:

> Since J. B. McLester in his study of the histories of pellagrins seen at the Hillman Hospital in Birmingham made the significant discovery that an appreciable number of these patients had been admitted the previous year under the diagnosis of neurasthenia, we have made an effort toward the early recognition of such cases of subclinical pellagra. Many of the patients recently studied could with some justice be called neurasthenic, but when given nicotinic acid and thiamin, with a diet appropriate for pellagra, they recovered their nervous stability and sense of well-being to a remarkable degree. I believe that with a good history, the prepellagrous state can be recognized without great difficulty and further progress of the disease stopped.

10. McLester, J. S.: Borderline States of Nutritive Failure, J. A. M. A. **112**:2110-2114 (May 27) 1939.

It now is well recognized that few cases of pellagra depend exclusively on the presence of a deficiency of nicotinic acid and that deficiency of thiamine is evident in most such cases. It is not improbable that many of the nervous and mental symptoms of pellagra depend primarily on the lack of sufficient thiamine in the dietary regimen.

CONCLUSIONS

1. A dietary supply of 0.95 mg. of thiamine (285 international units of vitamin B_1) was associated with no clear evidence of nutritional deficiency, but it provided less than a sufficient amount of this vitamin for the best nutritional state of the patient.

2. A climatologic factor may influence the rate of development of evidence of thiamine deficiency. A diet restricted to 0.15 mg. of thiamine (50 international units of vitamin B_1) was tolerated for one hundred and forty-seven days by 4 subjects who received it during the summer months. A similar diet given to 4 other subjects in the winter months could be tolerated for only eighty-eight days. Symptoms of thiamine deficiency developed earlier among the subjects whose diets were restricted during the winter months.

3. Physical activity affects the rate of development of evidence of thiamine deficiency. When diets were restricted to 0.15 mg. of thiamine, subjects who were more active experienced symptoms earlier and were more seriously affected later than those who were less active. The shortest time for the appearance of clear evidence of deficiency was twelve days; the longest, forty-eight days.

4. The disease induced by restricting the intake of thiamine differed from classic beriberi in that edema, cardiac dilatation and peripheral pain were absent. We are led to question whether thiamine is the vitamin the lack of which is responsible for these classic features of beriberi.

5. The early stage of the disease induced by restricting the intake of thiamine closely resembles neurasthenia; the later stage simulates anorexia nervosa. Therefore, we propose that states of thiamine deficiency, as these exist in our part of the country, where few cases of beriberi or pellagra are encountered, should be looked for principally in cases in which the diagnosis neurasthenia has appropriately been made.

PAIN IN THE SHOULDER AS A SEQUEL TO MYOCARDIAL INFARCTION

A. CARLTON ERNSTENE, M.D.
AND
JACK KINELL, M.D.
CLEVELAND

The development of persistent pain in the shoulder region in patients who have disease of the coronary arteries is sufficiently common to warrant more comment than it has hitherto received. The mechanism responsible for the pain has not been determined, but the frequency of its occurrence is such as to indicate more than a chance relationship to the attendant heart disease. The pain occurs most commonly as an aftermath of myocardial infarction, but it also develops at times in persons who have frequent and severe attacks of angina pectoris and who present no evidence of having suffered from earlier coronary occlusion. One or both shoulders may be affected, but the left shoulder is more commonly involved than the right. The pain lasts for several weeks or months and is usually increased by movement of the arm but is not influenced by walking. In patients who experience attacks of angina pectoris after coronary occlusion, the pain may be greatly increased during, and for some time after, the anginal seizures. Examination of the involved shoulder usually reveals limitation of movement, especially of abduction and external rotation, with tenderness about the joint or over the lateral aspect of the upper part of the arm. The common clinical picture is thus identical with that of periarthritis of the shoulder. At times, however, pain and a sensation of weakness are the only symptoms; there is no appreciable limitation of motion and no tenderness can be elicited by firm pressure. In a certain number of patients, also, changes similar to those of rheumatoid arthritis develop in other joints either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

MATERIAL AND RESULTS

The present report is based on a study of 17 cases of persistent pain in the shoulder region encountered in a series of 133 consecutive cases of myocardial infarcation (table). In 3 patients the pain in the shoulder

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Case No.	Sex	Age	Shoulder Affected by Radiation of Cardiac Pain	Location of Infarct	Shoulder Affected	Interval Between Coronary Occlusion and Onset of Persistent Pain in Shoulder	Duration of Pain in Shoulder	Angina Pectoris After Coronary Occlusion	Comments
1	M	40	0	Anterior	Left, right later	Left shoulder 5 months; right shoulder 9 months	8 months	0	Typical periarthritis
2	F	58	Left	?	Left	Coincident	3 months	+	Typical periarthritis
3	M	60	Left	Anterior	Left	Coincident	19 months	+	No limitation of movement
4	M	49	Right	Posterior	Both	3 months	18 months improved	+	Periarthritis; simultaneous development of rheumatoid arthritis involving fingers and knees
5	M	64	0	Anterior	Left	3 months	3 months unimproved	+	No limitation of movement
6	F	49	Left	Anterior	Right, left later	Right shoulder 4 months; left shoulder 7 months	9 months	0	Periarthritis; rheumatoid arthritis involving elbows, wrists, fingers and knees developed simultaneously with pain in right shoulder
7	M	57	Both	Anterior	Right	3 weeks	4 months	0	Typical periarthritis; later rheumatoid arthritis
8	M	65	Left	Anterior	Left	1 week	10 weeks	0	Persistent pain in left shoulder and left scapular region without limitation of movement
9	F	49	Left	Posterior	Left	Coincident	4 months unimproved	0	Mild periarthritis; associated numbness and weakness of left arm
10	M	49	Left	Anterior	Left	2 months	9 months	0	Mild periarthritis; simultaneous development of rheumatoid arthritis involving fingers
11	M	40	0	Anterior	Left	12 months	7 months unimproved	+	No limitation of movement
12	M	57	Left	Anterior	Left	18 months	3 months improved	+	No limitation of movement; in addition to painful shoulder, residual numbness and swelling of left hand after anginal attacks
13	M	76	Both	Anterior	Right	22 months	6 months improved	+	Periarthritis; simultaneous development of rheumatoid arthritis involving wrists and fingers
14	M	47	0	Posterior	Left	5 years	4 months	+	Typical periarthritis
15	M	59	0	Posterior	Both	8 years	9 months	+	Typical periarthritis
16	M	55	Left	Anterior	Both	See comment	6 months unimproved	+	Angina pectoris and persistent pain in shoulder for 1½ years before coronary occlusion; worse after occlusion
17	F	53	Both	Anterior	Both	See comment	2 years unimproved	+	Rheumatoid arthritis and persistent pain in shoulder for 6 years before coronary occlusion; pain in shoulder worse after occlusion

dated from the attack of coronary occlusion, and in 7 others it developed within five months after the attack. In 5 patients the pain did not appear until one to eight years after the coronary accident, but it is worthy of note that all of these patients had experienced frequent attacks of severe anginal pain since the time of the coronary occlusion. Two patients had suffered from the anginal syndrome for one and one-half and for six years respectively before the attack of coronary occlusion and for the same lengths of time had experienced practically constant pain in both shoulders. In both patients the pain in the shoulder had been more severe since the time of myocardial infarction.

The direction of radiation of the pain of coronary thrombosis appeared to be a factor of considerable importance in determining which shoulder was to be affected later. Periarthritis of the shoulder more commonly involves the right shoulder than the left.[1] In contrast to this, the persistent pain which develops with or after coronary thrombosis affects the left shoulder much more commonly than the right, and the frequency with which the left shoulder is involved corresponds approximately with the incidence of radiation of the pain of coronary occlusion to the left shoulder and arm. Of 8 patients in whom the pain of coronary occlusion radiated only to the left shoulder and arm, the persistent pain involved the left shoulder in 6 and both shoulders in 2. In the single patient in whom the pain of the acute attack radiated only to the right shoulder and arm, persistent pain subsequently developed in both shoulders. The pain of coronary occlusion radiated to both shoulders in 3 patients. In 2 of these the right shoulder subsequently became persistently painful, while the other patient had had practically constant pain in both shoulders, as well as frequent attacks of angina pectoris for six years before the occurrence of coronary thrombosis. In 5 patients the pain of coronary occlusion did not radiate beyond the thorax; in 3 of these the left shoulder subsequently became painful, while in the other 2 both shoulders were involved. Among the entire 17 patients, the left shoulder alone was the site of persistent pain in 9, the right shoulder alone in 2 and both shoulders in 6.

The site of the myocardial infarct did not appear to be of importance with relation to the localization of the persistent pain in the shoulder.

In approximately two thirds of the patients, examination of the involved shoulder revealed local tenderness either about the joint or over the lateral aspect of the upper part of the arm and moderate or marked limitation of movement, especially of abduction and external rotation. In 5 patients, however, the range of motion was normal in all directions and no local tenderness could be elicited. Roentgen

1. Dickson, J. A., and Crosby, E. H.: Periarthritis of the Shoulder: An Analysis of Two Hundred Cases, J. A. M. A. **99**:2252-2257 (Dec. 31) 1932.

examination was made of the affected shoulders of several patients, but in only 1 patient were calcific deposits found in the region of the subdeltoid bursa.

It is of interest that in 5 patients symptoms and local changes similar to those of rheumatoid arthritis appeared in other joints either at the same time as the development of the pain in the shoulder or shortly thereafter. One other patient had had pain in the shoulders and rheumatoid arthritis involving the fingers, elbows and back in association with angina pectoris for six years before the occurrence of coronary occlusion.

The known duration of the pain in the shoulder following myocardial infarction varied from less than three months to more than two years. In several instances the pain was still present at the time the patient was last heard from, so that no statement can be made concerning the maximum duration of symptoms. For the most part the pain seemed to pursue a self-limited course. In several patients the symptoms were not sufficiently severe to require special treatment. In the more severe disturbances, however, treatment consisted of the local application of heat by baking and diathermy and the oral administration of analgesics, but it usually was not possible to be sure that these measures shortened the duration of the disability.

The clinical course of the pain in the shoulder is exemplified in the following case report.

REPORT OF A CASE

A white man 57 years of age was seized with agonizing substernal pain while returning to his home from Florida by train. The pain radiated to both shoulders and down the inner aspects of both arms to the wrists. Two hypodermic injections of morphine sulfate gave only partial relief, and the pain persisted, but with gradually diminishing intensity, for twelve hours. The patient was admitted to the hospital twenty-four hours after the onset of the pain. At that time the temperature was 100.2 F., and the leukocyte count was 16,500 per cubic millimeter. The erythrocyte sedimentation rate was moderately elevated above the normal, and an electrocardiogram gave evidence of anterior myocardial infarction.

There was no recurrence of the substernal pain after the initial attack, and for three weeks the clinical course was entirely uneventful. The leukocyte count returned to normal on the seventh day, and the temperature did not rise above normal after the twelfth day. The erythrocyte sedimentation rate attained its maximum at the end of two weeks and then gradually became slower, but it did not reach a normal value until the end of the third month. Three weeks after admission to the hospital the patient began to complain of persistent pain in the right shoulder, at first mild and aching but gradually increasing in severity. Examination revealed an increasing degree of limitation of movement of the shoulder and tenderness over the lateral aspect of the upper part of the arm. Roentgenograms of the joint showed no pathologic changes. Diathermy and baking gave only partial and temporary relief from the pain. After three months the discomfort began to subside gradually, and by the end of the fourth month

it had disappeared entirely. Two months later, however, stiffness, pain on motion and tenderness developed in the hands and feet, and a diagnosis of rheumatoid arthritis was made. General measures of treatment were instituted, and all symptoms in the joints subsided after another two months.

COMMENT

The occurrence of persistent pain in the shoulder region as a sequel to myocardial infarction has been commented on by only a few observers. Howard,[2] Boas and Levy[3] and Leech[4] reported cases in which the clinical picture of the involved shoulder resembled that of periarthritis. Edeiken and Wolferth[5] also reported a series of cases, but their cases differed somewhat from those of the other observers inasmuch as the pain was not aggravated by ordinary movements of the arm and there was no local tenderness on pressure. Cases of both kinds are included in the present report. It is of interest that Edeiken and Wolferth estimated the incidence of the symptoms in the shoulder as in excess of 10 per cent among survivors of myocardial infarction. In the present series of cases of myocardial infarction the incidence of pain in the shoulder amounted to 12 per cent, but in approximately two thirds of this number the characteristic features of periarthritis of the shoulder were present. It may well be that the difference between the cases in which the condition resembled periarthritis and those in which there was no local tenderness or limitation of motion is one of degree only.

The mechanism by which the pain is produced is not known. Edeiken and Wolferth suggested an analogy to the causalgia which may follow obliteration of a peripheral artery. Boas and Levy suggested two possibilities: (1) that radiation of the anginal pain to a shoulder which was already the site of slight pain might, by summation, induce the painful discomfort or (2) that afferent pain impulses from the heart might lead to sensitization of the neurons whose fibers go to make up the brachial plexus. They expressed the opinion that the latter of these two possibilities is a more probable explanation than the former. It seems to us that there is still another possible mechanism, namely, that the symptoms develop as a result of relative disuse of the shoulder and abnormal tension of the muscles of the shoulder girdle. During the

2. Howard, T.: Cardiac Pain and Peri-Arthritis of the Shoulder, M. J. & Rec. **131**:364-365 (April 2) 1930.

3. Boas, E. P., and Levy, H.: Extracardiac Determinants of Site and Radiation of Pain in Angina Pectoris with Special Reference to Shoulder Pain, Am Heart J. **14**:540-554 (Nov.) 1937.

4. Leech, C. B.: Painful Shoulder in Association with Coronary Artery Disease, Rhode Island M. J. **21**:104-106 (July) 1938.

5. Edeiken, J., and Wolferth, C. C.: Persistent Pain in Shoulder Region Following Myocardial Infarction, Am. J. M. Sc. **191**:201-210 (Feb.) 1936.

period of strict rest in bed and the subsequent limitation of activity which are enforced on the patient who has had acute coronary thrombosis, the shoulder is used much less than normally. In addition, after the severe pain of coronary occlusion certain patients for a long time may unconsciously keep the muscles of the shoulder girdle on one or both sides in a state of abnormal tension as a protecting mechanism against the possible recurrence of pain. Tension of this kind might be expected to be greater on the side to which the pain of the coronary seizures radiated, and this theory would help to explain the relation between the direction of radiation of the cardiac pain and the site of the subsequent persistent symptoms in the shoulder. Once the pain has appeared in the shoulder, continued tensing of the muscles would be natural, and this tension in turn would explain the prolonged duration of the symptoms in so many patients. As matters stand at present, however, there is not sufficient evidence to enable one to state which of the above mechanisms is actually responsible for the development of the persistent pain.

There are certain practical reasons why this sequel to myocardial infarction is deserving of emphasis. Many patients when the persistent pain develops in the shoulder first interpret the symptoms as having resulted from some further injury to the heart. The physician is therefore consulted in alarm, and it obviously is of great importance that he be able to interpret the pain correctly. Furthermore, when one is consulted by a patient because of persistent pain in one or both shoulders, the possibility should be borne in mind that the trouble may have followed unrecognized coronary thrombosis. A careful cardiovascular history, therefore, should be taken, and this should include detailed questioning about recent attacks of "indigestion" or "gas." If the history is at all suggestive or if physical examination reveals abnormal cardiovascular findings, an electrocardiogram should be made. The tracing under such circumstances may show changes characteristic of myocardial infarction.

SUMMARY

The development of persistent pain in one or both shoulders is a relatively common sequel to myocardial infarction. The severity of the condition ranges from the clinical picture of typical periarthritis with intense pain and great limitation of motion to one of mild aching pain with a sensation of weakness but without loss of function. The left shoulder is affected more commonly than the right, and the symptoms persist for several weeks or months. In a few patients, changes similar to those of rheumatoid arthritis develop in other joints either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

The present report is based on 17 cases of persistent pain in the shoulder region encountered in a series of 133 consecutive cases of myocardial infarction. In 15 of these the pain dated from the attack of coronary occlusion or developed subsequent to the attack. In the other 2 the patients had suffered from angina pectoris and practically constant pain in both shoulders for a long time before the acute coronary attack. In both of them the pain in the shoulder increased in severity after the occurrence of myocardial infarction. In 6 of the 17 cases symptoms of rheumatoid arthritis involving other joints developed either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

The cause of the persistent pain in the shoulder region is unknown. The mechanisms which have been suggested as possible explanations in the past have been reviewed, and an additional hypothesis is proposed.

The practical significance of this sequel to myocardial infarction is pointed out.

INTERAURICULAR SEPTAL DEFECT

W. S. TINNEY JR., M.D.
LANCASTER, PA.

In February 1938 there were 2 patients in the Lancaster General Hospital at the same time, both of whom showed large interatrial septal defects at necropsy. The purpose of this paper is to present the 2 cases and to review the literature since 1934, at which time Roesler made an extensive clinical study and a complete review of the literature on this subject. He collected 62 cases, including a case of his own.

REPORT OF CASES

CASE 1.—A 76 year old white man, a locomotive engineer, was admitted to the hospital on Feb. 17, 1938, complaining of headache, poor vision and a heavy feeling over the front of the chest.

He had had a sore throat many times as a child, scarlet fever, "lung fever" (at age of 10 years) and pneumonia (in 1935). At the age of 18 years he had a "bad heart" and was in bed for over a year. At 21 he went west and worked for twenty years as a locomotive engineer and as an operator of steam shovels. For the next fourteen years he was a postal clerk. During all this time he had no cardiac or other complaints.

About midnight on January 10 he was awakened in a terrible fright; he was short of breath and could not feel his pulse. This lasted about five minutes, after which he felt much better. His usual weight, 140 pounds (63.5 Kg.), had fallen to 110 pounds (49.9 Kg.) during the past year. He had had a nonproductive cough, edema of the ankles and increasing dyspnea for two weeks prior to admission.

On physical examination moderate clubbing of the fingers and considerable dyspnea were noted. There was marked scoliosis to the left in the upper part of the thoracic region, and the ribs on the right of the sternum protruded markedly. Marked cervical venous pulsations were noted. There was a diffuse and strong thrust at the cardiac apex. No thrills were felt. The heart was markedly enlarged to the left, and the point of maximal intensity was felt in the anterior axillary line. The apex was beyond the anterior axillary line on percussion. The rhythm was irregular; the rate was 80. A loud systolic murmur was heard all over the precordium but was heard best at the apex and was transmitted to the axilla. There was marked peripheral sclerosis. The blood pressure was 144 systolic and 64 diastolic. The liver was palpable 3 cm. below the costal margin.

The value for hemoglobin was 58 per cent. There were 3,560,000 red cells and 5,000 white cells per cubic millimeter of blood. There was a faint trace of albumin in the urine. The Wassermann reaction of the blood was negative.

An electrocardiogram taken February 18 showed a slurred and low voltage QRS complex in all leads. The rhythm was nodal, with a tendency to bigeminy.

The clinical impression was that of rheumatic cardiovascular disease with decompensation, mitral insufficiency and marked myocardial dilatation. The patient became rapidly more dyspneic and died on February 23.

Autopsy was performed by Dr. Louisa E. Keasbey. The main interest centered about the heart and lungs. The lungs were pushed back out of view by the greatly enlarged heart. The pulmonary artery was greatly enlarged.

The pericardium was opened and was seen to contain a slight excess of fluid. The heart was enormously enlarged, measuring 22 cm. in its transverse diameter (the chest measured 31 cm.). The heart weighed 860 Gm. As viewed in situ there was marked rotation, so that the left ventricle was not apparent to inspection. In situ there was observed a very large defect in the interauricular septum. It measured 4.5 cm. in length; it was oval, with somewhat cordlike edges, resembling a greatly enlarged foramen ovale which was devoid of any valvelike flap of tissue. The right side of the heart was enormously enlarged, dilatation having great preponderance over hypertrophy. The right auricle measured 12.5 cm. in

Fig. 1.—Defect in the interauricular septum.

diameter and the tricuspid valve 14.5 cm. in circumference. The right ventricle was greatly dilated, with a maximum thickness of 1 cm. The pulmonary artery was exceedingly enlarged, measuring 10 cm. in circumference at the pulmonary valve and 9 cm. at the point of bifurcation. The inferior vena cava was greatly dilated and measured 7 cm. in circumference at the entrance into the heart. The left ventricle was on the posterior surface of the heart and did not appear to participate in the enlargement. The wall of the left ventricle was 1.5 cm. thick. The aortic valve was 6 cm. in circumference. The mitral valve was 11 cm. in circumference. All surfaces of the heart were soft and pliable and were free of any evidences of endocarditis. The coronary arteries showed slight sclerotic changes and were rather large, the main vessel being 1 to 1.5 cm. in circumference. The aorta showed evidence of atheromatous plaques, and moderate arteriosclerosis was present in the smaller vessels.

The liver showed slight evidence of congestion of the nutmeg type. It was not greatly enlarged.

The kidneys were markedly congested, and arteriosclerosis was noted. The cortices were congested and swollen.

The anatomic diagnoses were interauricular septal defect and chronic passive congestion.

CASE 2.—A 47 year old white man was admitted to the Lancaster General Hospital on Feb. 4, 1938, complaining of weakness and shortness of breath.

He had suffered from typhoid fever in boyhood. A previous attack of cardiac decompensation had occurred three years prior to his admission to the hospital. There had been a "nervous breakdown" at the age of 18 years, following heavy drinking. There was no history of rheumatic fever.

His present illness had begun on January 15, after an alcoholic debauch. He had soon become weak and short of breath, and a cough, productive of a rather profuse greenish material, had developed.

The patient was well developed, showing slight dyspnea at rest. Fine rales were heard at the bases of both lungs, and there was marked dulness at the base of the right lung. There were no thrills. The heart was markedly enlarged on percussion, the left border being 14 cm. from the midsternal line in the fifth interspace. The sounds were very weak and distant; the rhythm was regular. A short systolic murmur was heard at the mitral area but was fleeting. The pulmonic second sound was greater than the aortic. The blood pressure was 100 systolic and 84 diastolic. The pulse rate was 90. The liver was very tender and extended almost to the umbilicus. There were marked edema of the extremities and slight clubbing of the fingers.

The value for hemoglobin was 82 per cent. There were 4,410,000 red cells and 8,000 white cells per cubic millimeter of blood. The Wassermann reaction of the blood was negative.

An electrocardiogram taken February 5 showed a 2:1 auricular flutter. Lead I showed a flat T wave, and there was low amplitude of the QRS complex in leads II and III. On February 17 the electrocardiogram showed a definite Q wave in lead III. On March 7 the electrocardiogram showed that auricular flutter had continued, uninfluenced by light quinidine therapy.

Fluoroscopic examination on February 5 showed tremendous cardiac hypertrophy and dilatation. The apex of the left ventricle was in the anterior axillary line. The right border was halfway to the right axillary line. Both sides of the diaphragm were almost completely obscured by the cardiac enlargement. The lung fields were very cloudy because of passive congestion. The aorta was slightly widened.

During his first three weeks in the hospital the patient appeared to improve, although a septic temperature and a totally irregular rhythm continued. However, he never regained full compensation. A second fluoroscopic examination, done on March 7, showed a large amount of fluid, filling at least two thirds of the right side of the thorax. The heart was tremendously enlarged; the amplitude of the pulsations was small. The apex of the heart was almost at the left costal margin. In the right anterior oblique position the posterior portion of the mediastinum was obscured by fluid. The aortic shadow was widened, hazy and difficult to visualize. In the left anterior oblique position there was extreme cardiac dilatation; the amplitude was very small. Thoracenteses on the right were performed on March 3, 17 and 22.

The clinical impression was that of myocardial hypertrophy and decompensation of unknown cause, with cirrhosis of the liver.

Autopsy was performed by Dr. Louisa E. Keasbey. There was no fluid in the left side of the chest, but 1,000 cc. of amber fluid was present on the right. The right lung was edematous, weighing 730 Gm.; the left weighed only 470 Gm.

The pericardial cavity was opened, and a slight excess of pericardial fluid was noted. The heart was greatly enlarged. The transverse diameter in situ was 20 cm.; the diameter of the chest was 30 cm. The heart weighed 585 Gm. There were two milk spots on the anterior surface. The enlargement was greater on the right side, with a hypertrophied and dilated right ventricle and right auricle. When the heart was opened a patent interatrial septum was seen. The long diameter measured 4.5 cm. This was partially occluded by a flap which acted in a valvelike fashion. With the valve closed, one third of the communication remained patulous. The diameters of the valves were as follows: tricuspid, 11 cm.; pulmonary, 8.5 cm., and mitral, 10.5 cm. The diameter of the pulmonary artery at the hilus of the lung was 2.5 cm. Grossly the valves appeared in good condition. The myocardium appeared somewhat degenerated and was soft and flabby. The aorta was slightly calcified. There were no mural thrombi. The coronary vessels were of good size and slightly sclerotic.

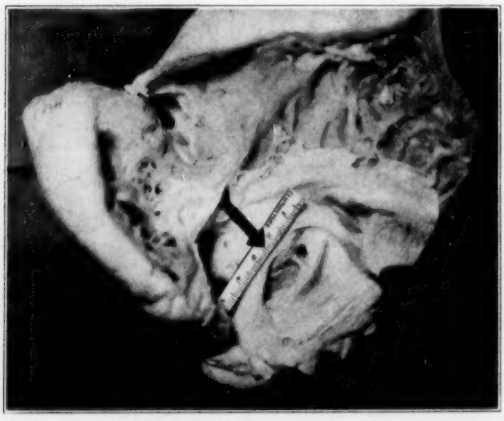

Fig. 2.—Patent interatrial septum.

The spleen was enlarged, weighing 215 Gm. It was pale and somewhat fibrotic. The kidneys were markedly enlarged and were pale. The liver was greatly enlarged, weighing 2,520 Gm. It had a typical nutmeg appearance. The gallbladder contained a small amount of green bile. The bile ducts were patent.

The pathologic diagnoses were: patent interatrial septum; congestive heart failure with cardiac hypertrophy and dilatation; hydrothorax on the right, and early cirrhosis of the liver.

All cases of interatrial septal defect which I could find in the literature since 1934 were reviewed, and a few of the results are presented (see table). Cases of slight patency of the foramen ovale were not included, since this is the commonest of all congenital cardiac defects, the incidence, according to Patten, being approximately 25 per cent.

An attempt was made to include only those cases in which there existed a defect of about 1 cm. or larger, but since the exact measurements were not always reported a few cases were also included in which were observed the following typical pathologic features: (1) a widely patent foramen ovale; (2) marked hypertrophy and dilatation of the right auricle and ventricle; (3) relative enlargement of the pulmonary artery and its branches, and (4) relative smallness of the left ventricle and the aorta.

Data in Twenty-Two Cases from the Literature

Author	Date	Patient's Age	Patient's Sex	Size of Aorta	Size of Pulmonary Artery	Description of Defect
1. McGinn and White....	1933	56	M	.....	10.5 cm.	2.4 by 1.5 cm.
2. Yater, Barrier and McNabb	1934	57	F	Small	Very large	
3. Mitchell and Bauer....	1934	40	M	5 cm.	8.5 cm.	1 by 3.5 cm.
4. Joules	1934	37	F	Little finger	Aneurysm	Ostium secundum
5. Cesari	1935	30	F	1.6 cm.	2.5 cm.	2 by 1.6 cm.
6. Gibson and Roos.....	1935	12	M	Hypoplastic	Very large	4 by 3 cm.
7. Gibson and Roos.....	1935	25	M	.....	.....	4 cm.
8. Sailer.....	1936	67	M	Small	Large	Ostium primum, 3 cm.
9. McLeod	1936	33	F	.....	Conus very large	2 by 1.1 cm.
10. Cossio and Berconsky	1936	25	M	.....	.....	Large
11. Lutembacher	1936	61	..	2.5 cm.	6.5 cm.	Wide open
12. Lutembacher	1936	22	F	2.5 cm.	4 cm.	.....
13. Arana and Aguirre....	1936	11	M	4.7	6.5 cm.	1.5 by 1.4
14. Tarnover and Woodruff	1936	77	M	2/3 size of pulmonary artery	10.5 cm.	4 cm.
15. Cossio and Arana.....	1937	..	M	1.8 cm.	3.0 cm.	4.5 cm.
16. Cossio and Arana.....	1937	53	M	.....	.....	2.1 by 2.3 cm.
17. Cossio and Arana.....	1937	13	F	4.5 cm.	6.5 cm.	1.4 by 0.4 cm.
18. Kutumbiah and Rao..	1937	20	M	5.7 cm.	10.5 cm.	4 by 3 cm.
19. Taussig, Harvey and Follis	1938	47	M	4.5 cm.	9 cm.	.3 cm.
20. Taussib, Harvey and Follis	1938	8¾	M	5.8 cm.	6.4 cm.	2 cm.
21. Taussig, Harvey and Follis	1938	47	F	6.5	2 times size of aorta	5 cm.
22. Taussig, Harvey and Follis	1938	9½	F	3.5 cm.	6.5 cm.	3 cm.

ETIOLOGY

Most persons agree that the characteristic pathologic changes in the heart are consequent on the interatrial septal defect and consider this the primary lesion. The right side of the heart is so disproportionately dilated and hypertrophied because the blood is shunted from the left to the right atrium, thus depriving the left side of the heart of its usual load.

Lutembacher claimed that mitral stenosis in these cases is of congenital origin. By producing an increased pressure in the left auricle, the stenosis would ultimately cause a shunt of blood from the left to the right auricle through the patent foramen, which would, therefore, never

be able to close. There are many serious objections to this theory, the best being that in a fair percentage of cases of rather marked interatrial septal defect the condition is unaccompanied with mitral stenosis. Both cases presented here illustrate this point.

A congenitally hypoplastic aorta would also produce an increased pressure in the left side of the heart and have an effect similar to that of mitral stenosis. This should theoretically keep the foramen ovale open by a left to right shunt. However, in these 2 cases the aorta is not truly hypoplastic but only relatively smaller than the pulmonary artery.

PATHOLOGIC PICTURE

Originally the atrium is a single cavity. A septum grows down from the superior portion of this cavity to divide it into a right and a left auricle. This septum, known as the primary septum, meets a much smaller septum, known as the endocardial cushions, which has grown up from the inferior portion of the single atrium. When these two septums meet, the primary communication between the auricles, the ostium primum, is obliterated. The communication between the atria is reestablished when an opening is formed in the primary septum, known as the foramen ovale, or ostium secundum. A little later in fetal development another septum, known as the septum secundum, grows down to the right of the primary septum and after birth eventually fuses with the primary septum, thereby obliterating the foramen ovale. Any failure in the union of the primary septum and the inferior portion of the auricle causes a persistent ostium primum. Any failure of union between the primary septum and the septum growing down to the right of it causes a persistent ostium secundum or a patent foramen ovale.

The typical pathologic changes are well exemplified in these 2 cases. I have classified both as cases of typical persistent ostium secundum.

The right auricle and ventricle in both cases were markedly hypertrophied and dilated, dilatation exceeding hypertrophy. In both the left side of the heart was relatively small. There were also marked dilatation and hypertrophy of the pulmonary artery, causing it to exceed the size of the aorta in both cases, although the aorta was only relatively smaller and could not be considered truly hypoplastic.

There was no pathologic evidence of any chronic valvular defects in the heart in either case. This is rather unusual, since Roesler found that in three fourths of his series of 62 cases the condition was complicated by chronic valvular defects. In 15 of the 22 cases which I reviewed there were complicating valvular lesions. In 11 of these the lesion was mitral stenosis.

CLINICAL PICTURE

Approximately 61 per cent of all interatrial septal defects are found in females. Both patients described here were men.

Cyanosis is present only in the very late stages of this disease, when the increased pressure in the right atrium causes a right to left shunt. One third of the blood must be shunted before cyanosis is produced. The condition has therefore been classified by Abbott as *cyanose tardive*.

In contrast to the picture of many other congenital cardiac diseases, clubbing is rarely found and, when present, is usually slight in cases of uncomplicated interatrial defects. Very slight clubbing was found in only 3 of the cases reviewed. Both patients described here showed clubbing.

Thrills are an inconstant finding, being recorded in only 8 of the 22 cases reviewed. In 7 the thrill was systolic; in 1 it was systolic and diastolic. Murmurs are variable. The commonest finding is a systolic murmur in the third left interspace, rather closely simulating that associated with *maladie de Roger* except that it is usually slightly higher and not so intense. As would be expected with any condition in which such a large burden is placed on the right side of the heart, the pulmonic second sound is usually greater than the aortic, although this finding is of little diagnostic value in those cases complicated by mitral stenosis.

The heart is enlarged both to the right and to the left of the sternum, the enlargement to the left being caused by hypertrophy and dilatation of the right auricle and ventricle plus counterclockwise rotation of the heart.

Since the pathologic process is present from birth, most patients show a deformity of the left side of the chest.

Pulsation of the veins of the liver and of the neck is common, particularly when the condition is complicated by a pathologic condition of the tricuspid valve.

The antemortem diagnosis of this condition is rarely made, but it can be greatly facilitated by roentgen and fluoroscopic examinations, which reveal an enlarged, globular heart (most of the enlargement being in the right auricle and right ventricle), very wide hilar shadows (often pulsating and mistaken for tuberculosis or tumor), a greatly enlarged pulmonary arch and a very small aortic knob. The contour of the left side of the heart is formed almost entirely by the right ventricle. Counterclockwise rotation of the heart takes place. Contrary to the opinion of Lutembacher, the typical *"coeur en sabot"* configuration is not seen.

The electrocardiogram usually shows right axis deviation and high P waves. Auricular fibrillation is common.

PROGNOSIS

The prognosis of this condition is not necessarily bad, as is well substantiated by the ages of these 2 patients. The average age of

the patients in Roesler's series was 36 years. The average age of the patients in the 22 cases reviewed since 1934 was 34.8 years. If the 2 patients described here are included the average age is raised to 37 years.

Since three fourths of all interatrial septal defects are complicated by chronic valvular lesions, the prognosis of the defect alone is rather difficult to ascertain. However, Roesler found that the presence of a chronic valvular lesion did not materially affect the prognosis. The oldest patient described in the literature since 1934 was the patient of Tarnover and Woodruff, who lived to be 77. Our first patient was 76.

COMPLICATIONS

Although a superimposed rheumatic infection is one of the most frequent complications, no pathologic evidence of such an infection was found in the heart in either case. In 68 per cent of the 22 cases reviewed there were chronic valvular lesions. In 50 per cent there was mitral stenosis.

Roesler stated that chronic pericardial disease is practically absent. He was able to find only 1 case in his review, and the patient had chronic extensive pulmonary tuberculosis. There have been 3 cases reported since Roesler's review in which chronic pericarditis was present as a complication.

There have been no cases reported in which subacute bacterial endocarditis was present, although this complication is frequently found in association with other congenital malformations of the heart.

Auricular fibrillation is rather rare in association with other congenital malformations of the heart, but it is very common with interatrial septal defect. In 7 of the 22 cases which we reviewed there was auricular fibrillation; in 3 there was auriculoventricular block, and in 2 of the latter the Stokes-Adams syndrome was observed.

Pulmonary infections and emboli occur very often and, together with cardiac decompensation, usually cause the death of the patient.

SUMMARY AND CONCLUSIONS

Two cases of uncomplicated interatrial septal defect are presented. The respective ages of the patients were 76 and 47.

A review of the literature since 1934 has revealed 22 cases of interatrial septal defect. Roesler's review in 1934 included 62 cases. This brings the total number of cases reported to 86, including the 2 reported here.

The characteristic pathologic features in addition to the septal defect are marked hypertrophy and dilatation of the right auricle, the right ventricle and the pulmonary artery. The left auricle, the left ventricle and the aorta are all relatively small.

The only way to be sure of a correct diagnosis is by roentgen or fluoroscopic examination. There are four characteristic features: increased hilar shadows, great enlargement of the right side of the heart, a small aortic knob and a very large pulmonary conus.

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RELATIVE SIGNIFICANCE OF CONCENTRATION OF INORGANIC SULFATE IN THE SERUM AND OF ITS RENAL CLEARANCE

WITH SPECIAL REFERENCE TO DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION

ARNOLDUS GOUDSMIT Jr., M.D.
Fellow in Medicine, the Mayo Foundation
AND
NORMAN M. KEITH, M.D
ROCHESTER, MINN.

The accumulation of inorganic sulfate in human serum above normal limits in advanced stages of renal disease was first observed by Denis [1] in 1921. Subsequent work by various groups of investigators (Denis and Hobson; [2] Loeb and Benedict; [3] Cope; [4] Hayman and Johnston [5]) substantiated these observations. Wakefield, Power and Keith [6] pointed out that sulfate, the concentration of which normally is not in excess of 5.5 mg.[7] per hundred cubic centimeters of serum, in an appreciable number of cases actually is the first substance to accumulate in the blood of patients with early renal insufficiency. Macy,[8] amplifying the scope of the problem, investigated the clearance of inorganic sulfate. He found a

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From the Division of Medicine, the Mayo Clinic.

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certain number of patients in whom renal damage could be expected to exist whose clearance of inorganic sulfate was less than 20 cc. per minute (which he considered the lower limit of normal), whereas with none of the other tests of renal function studied were the results considered indicative of diminished capacities of the kidney. Curiously enough, a few instances were observed in which retention of inorganic sulfate in the serum had taken place without its rate of excretion as measured by the sulfate clearance test having fallen below normal limits.

Apparent inconsistencies of this nature continue to be observed from time to time. Since not enough fundamental facts about the mechanism of excretion of the sulfate ion were available to explain the anomalous situation, one of us (Goudsmit), in collaboration with Power and Bollman,[9] made a study of various factors which might influence its rate of excretion in dogs. Among other features, their findings revealed that the sulfate clearance was greatly increased by relatively small increases in the level of sulfate in the plasma, produced by intravenous injection of sodium sulfate. Thus, raising the normal concentration of plasma sulfate 100 per cent brought about an increase of clearance of approximately 500 per cent. This is in agreement with the earlier observations of White and Monaghan,[10] who established this relation qualitatively in experiments on the dog.

In man, sulfate clearance similarly undergoes an increase after the concentration of sulfate in the plasma has been raised by intravenous administration of sodium sulfate (Hayman and Johnston;[5] Power, Goudsmit and Keith [11]). This increase is relatively smaller than that observed in the dog. Cope, on the other hand, was unable to observe an increase of the clearance of inorganic sulfate after its concentration in the plasma had been nearly doubled by oral administration of sodium sulfate. However, the value for normal clearance of endogenous sulfate in man reported by this author is considerably greater than that usually found in publications of other workers in the field.

METHODS OF STUDY

General Outline of Investigation.—The question thus arises whether the increased concentration of sulfate in the plasma in patients with renal disease may not in itself be the cause of the increased sulfate clearance seen occasionally under these circumstances. In an attempt to find an answer, we set out to study a group of patients with values for inorganic

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sulfate in excess of the upper limits of normal, or 5 mg. per hundred cubic centimeters of serum (group A), and to compare the sulfate clearances with those observed in a control group (B) of patients in whose cases values for serum sulfate of less than 5 mg. per hundred cubic centimeters were observed. In order to have more complete data in regard to renal functional changes in both these groups, values for urea clearance were obtained at the same time as those for sulfate clearance. The ratio of sulfate clearance to urea clearance was then calculated for each individual clearance period.

The selection of the cases was accomplished as follows: From the records of patients for whom sulfate clearance had been determined between Jan. 1 and Oct. 8, 1938, inclusive, all those with (1) values for inorganic sulfate in the serum exceeding 5 mg. per hundred cubic centimeters and (2) a rate of flow of urine of at least 2 cc. per minute were chosen for group A (24 patients). During this period, 194 determinations of sulfate clearance showing a rate of urinary flow of at least 2 cc. per minute were performed on patients for whom a value for inorganic sulfate of less than 5.0 mg. per hundred cubic centimeters of serum had been recorded. From their much larger number 26 were taken to form group B. In the case of each, a test usually had been made on the same day as one of the observations in group A.

When we checked back on the cases of the patients represented, they appeared to include 38 cases of diffuse arteriolar disease with hypertension and 11 cases of miscellaneous renal disease. In 1 case there was neither hypertension nor evidence of renal disease. The essential data collected are summarized in table 1.

Detailed Renal Functional Analysis.—For the purpose of a closer analysis, renal efficiency has been studied in each of the clinical groups. "Normal" function of the kidney was considered to exist (1) so long as the blood urea was maintained at a concentration not exceeding 46 mg. per hundred cubic centimeters;[12] (2) so long as the urea clearance measured 50 cc. per minute or more;[13] (3) so long as the value for

12. Only very rarely did the concentration of urea in the blood exceed this figure in MacKay and MacKay's extensive series of "normals" (MacKay, E. M., and MacKay, L. L.: The Concentration of Urea in the Blood of Normal Individuals, J. Clin. Investigation **4**:295-306 [June] 1927).

13. Usually 60 cc. per minute is cited as the lower limit of the normal maximal blood urea clearance, and our nonconformance to this "accepted" figure is deliberate. At the Mayo Clinic we have not made it a practice to correlate urea clearance to body build, for example, surface area, and then express it as "per cent of normal." This probably is in part responsible for the fact that we are frequently confronted with values between 50 and 60 cc. per minute without being able to detect renal or vascular disease in the patient investigated. An additional reason for our indulgence in this respect is the fact that the maximal urea clearance of one of us is definitely below 60 cc. per minute.

TABLE 1.—*Excretion of Sulfate and of Urea as an Index of Renal Function: A Comparative Analysis (Fifty Patients)*

Case No.	Sex	Age	Serum Sulfate, Mg. per 100 Cc.	Sulfate Clearance, Cc./Min.	Blood Urea, Mg. per 100 Cc.	Urea Clearance, Cc./Min.	Urine Volume, in 1 Hr., Cc.	Ratio of Sulfate Clearance to Urea Clearance	Diagnosis
19	M	51	14.6	11.3	148	10.8	142	1.05	Chronic nephritis of mixed type; multiple myelomas
5	M	56	12.0	21.8	120	15.5	250	1.41	Chronic glomerulonephritis (?) with mild secondary vascular disease and anemia
12	F	58	11.5	40.5	56	49.2	153	0.82	D. A. D.* group 3*
20	F	33	9.9	13.6	110	12.4	210	1.10	Chronic glomerulonephritis with mild secondary vascular disease
1	M	52	8.1	12.1	98	15.1	307	0.80	Chronic glomerulonephritis with mild secondary vascular disease
24	M	43	6.8	55.9	76	56.6	250	0.99	D. A. D. group 4; early congestive heart failure
26	F	62	6.8	13.0	36	46.1	245	0.28	D. A. D. group 2
14	M	52	6.7	24.2	62	26.6	140	0.91	D. A. D. group 2 with congestive heart failure
9	F	60	6.4	21.9	50	35.2	390	0.62	D. A. D. group 3
32	M	32	6.3	23.2	52	20.5	126	1.13	D. A. D. group 4
40	M	48	6.3	26.5	48	40.2	295	0.66	D. A. D. group 3
38	M	40	6.1	22.3	36	55.8	568	0.40	D. A. D. group 3
45	M	46	6.1	33.7	68	34.9	198	0.97	D. A. D. group 4
42	M	52	6.0	78.0	34	75.0	300	1.04	D. A. D. group 2; generalized arteriosclerosis; residual hemiplegia; "respiratory infection"
16	M	67	5.9	33.9	52	35.9	238	0.94	D. A. D. group 3
36	M	67	5.8	18.4	40	33.5	222	0.55	D. A. D. group 2; gout (?)
3	F	50	5.7	43.8	39	67.6	145	0.65	D. A. D. group 2; considerable edema both lower extremities (neither cardiac nor nephritic)
29	M	59	5.6	49.0	20	69.6	245	0.70	D. A. D. group 2, with general arteriosclerosis; recent cerebrovascular accident
34	M	36	5.6	27.0	58	28.5	126	0.95	Nephritis (?); diabetes mellitus,† grade 3; hyperlipemia; generalized arteriosclerosis
43	F	49	5.6	14.4	62	24.2	287	0.60	D. A. D. group 3
22	F	48	5.6	21.7	42	34.5	347	0.63	D. A. D. group 4
49	M	55	5.5	58.0	46	86.4	210	0.67	D. A. D. group 2, with considerable arteriosclerosis
47	M	48	5.1	28.2	40	60.3	225	0.47	D. A. D. group 4, with myocardial insufficiency
7	M	73	5.1	89.2	52	43.6	125	2.05	D. A. D. group 2, with auricular fibrillation and myocardial failure
6	F	19	4.9	20.6	30	30.7	420	0.67	Chronic glomerulonephritis with mild secondary anemia
21	F	40	4.4	26.2	54	40.2	180	0.65	D. A. D. group 1; obesity; congestive heart failure
11	M	57	4.4	14.5	22	48.9	275	0.30	D. A. D. group 1
28	M	66	4.2	23.1	27	36.3	243	0.64	D. A. D. group 2
35	F	58	4.2	14.2	24	20.1	124	0.71	D. A. D. group 2; nephritis latent diabetes with diabetic retinitis
4	F	60	4.0	11.6	15	47.2	145	0.25	D. A. D. group 2
2	M	56	3.9	26.6	38	51.5	318	0.52	D. A. D. group 3
33	F	57	3.9	23.0	30	55.5	280	0.41	D. A. D. group 3
41	M	29	3.9	37.6	38	90.4	430	0.42	Transient albuminuria
37	M	43	3.9	38.5	42	55.7	134	0.69	D. A. D. group 1
23	F	18	3.8	20.0	16	47.7	660	0.42	Toxic (?) nephritis; degenerative hepatitis
46	M	44	3.8	46.0	30	63.4	364	0.73	Essentially normal

TABLE 1.—*Excretion of Sulfate and of Urea as an Index of Renal Function: A Comparative Analysis (Fifty Patients)—Continued*

Case No.	Sex	Age	Serum Sulfate, Mg. per 100 Cc.	Sulfate Clearance, Cc./Min.	Blood Urea, Mg. per 100 Cc.	Urea Clearance, Cc./Min.	Urine Volume, in 1 Hr., Cc.	Ratio of Sulfate Clearance to Urea Clearance	Diagnosis
8	M	52	3.7	16.2	33	20.4	150	0.79	D. A. D. group 3
39	F	52	3.7	28.0	36	50.1	282	0.56	Chronic unilateral pyelonephritis; chronic lymphatic leukemia
13	M	53	3.6	32.0	26	58.8	320	0.54	Mild urinary tract infection; previous nephrectomy; diabetes mellitus grade 3-4
31	M	66	3.6	23.2	42	33.4	209	0.69	D. A. D. group 2; generalized arteriosclerosis; previous transurethral prostatic resection
27	M	48	3.6	24.4	28	55.8	200	0.44	D. A. D. group 2
50	F	70	3.6	28.1	26	22.8	145	1.23	D. A. D. group 2; recent cerebral vascular accident
18	F	40	3.4	13.5	24	17.2	230	0.79	D. A. D. group 2
25	F	58	3.2	70.0	30	62.7	800	1.12	D. A. D. group 2; adenomatous goiter without hyperthyroidism
48	F	51	3.1	32.0	18	51.2	355	0.63	D. A. D. group 2
44	F	20	3.1	14.1	24	27.2	240	0.52	Chronic glomerulonephritis (latent)
10	M	35	2.9	48.9	32	83.3	506	0.59	D. A. D. group 1
15	F	63	2.8	38.4	30	33.9	336	1.13	D. A. D. group 2, arteriosclerotic type; thrombosis of central retinal vein
30	F	52	2.8	38.5	24	46.4	330	0.83	D. A. D. group 2
17	M	54	2.6	50.8	18	87.5	300	0.58	D. A. D. group 1; diabetes mellitus grade 3

* "D. A. D." stands for diffuse arteriolar disease with hypertension of groups 1, 2, 3 and 4, respectively, according to Keith and Wagener's classification. Group 4 corresponds to "malignant hypertension."

† Diabetes mellitus grade 2 denotes the stage in which a quantitative diabetic diet alone allows the adult patient to remain essentially nonglycosuric. Grade 3 indicates that the administration of 30 units of insulin or less per twenty-four hours is necessary. All patients requiring more than 30 units of insulin per twenty-four hours are classified as belonging to group 4.

serum sulfate did not exceed 5 mg. per hundred cubic centimeters,[14] or (4) so long as sulfate clearance amounted to a minimum of 25 cc. per minute.[15] An analysis of the frequency with which renal sufficiency or insufficiency was encountered is summarized in table 2.

All clearance studies were conducted in the manner described by Macy. The values for sulfate were determined according to the method of Power and Wakefield; those for urea, essentially according to the method of Van Slyke and Cullen.[16]

14. Described in the introductory paragraphs of this paper.

15. Macy considered 20 cc. per minute the lower limit of normal sulfate clearance. In the present article the dividing line between "normal" and "pathologic" has been raised in accordance with our added clinical experience. It happens that in the complete series the number of patients with values for sulfate clearance of less than 25 cc. per minute approximately equals the number of cases in which an increased value of sulfate in the serum was encountered.

16. Van Slyke, D. D., and Cullen, G. E.: The Determination of Urea by the Urease Method, J. Biol. Chem. **24**:117-122, 1916.

RESULTS

Clinical Correlation.—A summary of the essential findings relating to the apparent ability of the kidneys of the patients studied to excrete urea and inorganic sulfate is presented in table 2. The group of patients with renal disease was too small and etiologically and clinically too heterogeneous for further analysis.

Of the 38 patients with hypertension, the majority had been hospitalized for closer evaluation of their condition, for the treatment of complications or for the management of nonrelated conditions. Of these, 24

TABLE 2.—*Data Pertaining to Renal Function in a Group of Thirty-Eight Patients with Diffuse Arteriolar Disease with Hypertension and Eleven Patients with Renal Disease*

	Number of Patients with		
	Hypertension, Groups 1 and 2†	Hypertension, Groups 3 and 4†	Renal Disease
Urea concentration in blood			
46 mg. per 100 cc. and less	21	6	7
More than 46 mg. per 100 cc.	3	8	4
Impaired renal function,* percentage	13	57	36
Urea clearance			
50 cc. per minute and more	10	5	3
Less than 50 cc. per minute	14	9	8
Impaired renal function,* percentage	58	64	73
Inorganic sulfate concentration in serum			
5 mg. per 100 cc. and less	16	3	6
More than 5 mg. per 100 cc.	8	11	5
Impaired renal function,* percentage	33	78	45
Inorganic sulfate clearance			
25 cc. per minute and more	14	7	4
Less than 25 cc. per minute	10	7	7
Impaired renal function,* percentage	42	50	64
Total number of patients	24	14	11

* "Impaired renal function" refers to the percentage of instances in which impaired renal function was demonstrated by test immediately above in the table.

† The different groups of hypertension refer to the classification of Keith and Wagener.

were classified as having diffuse arteriolar disease with hypertension groups 1 and 2 (the less severe types according to Keith and his associates [17]), and 14 were classified as having diffuse arteriolar disease with hypertension groups 3 and 4 (groups having a serious prognosis). One patient, though similar in many respects to patients with the more serious types of hypertension, failed to show enough retinitis to be truly representative of group 3 and has been included as belonging to group 2.

17. Keith, N. M.; Barker, N. W., and Kernohan, J. W.: Histologic Studies of the Arterioles in Various Types of Hypertension, Tr. A. Am. Physicians **46**: 66-70, 1931. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**:332-343 (March) 1939.

Concentration of Sulfate in the Serum.—The comparative analysis of the level of renal function associated with these groups of hypertension is especially interesting (table 2). No matter what criterion is used, it appears to be the rule that the excretory powers of the kidneys are diminished in patients with the severe degrees (groups 3 and 4) of diffuse arteriolar disease with hypertension (notable individual exceptions can be found in table 1), and apparently a most significant difference between the two groups is related to the concentration of sulfate in the serum. In the cases of 16 out of the 19 patients in whom a concentration of 5 mg. or less per hundred cubic centimeters of serum was encountered, diffuse arteriolar disease with hypertension group 1 or 2 was diagnosed, and only 33 per cent of all patients with hypertension group 1 or 2 showed the presence of serum sulfate in increased amounts. Conversely, of all the patients who had diffuse arteriolar disease with hypertension groups 3 and 4, 79 per cent, or 4 of every 5, had a concentration of sulfate above 5.0 mg. per hundred cubic centimeters of serum.

Sulfate Clearance.—The incidence of normal and abnormal values for sulfate clearance is evident from a consideration of the last line but one (table 2); of the patients with diffuse arteriolar disease with hypertension groups 1 and 2, 42 per cent showed diminished sulfate clearance. However, in patients with diffuse arteriolar disease with hypertension groups 3 and 4, of whom approximately two and one-half times as great a percentage showed increased sulfate in the serum, there was hardly any higher incidence of diminished sulfate clearance. It is thus remarkable that the proportion of patients showing retention of sulfate (79 per cent) is considerably in excess of the proportion (50 per cent) showing diminished sulfate clearance. In other words, retention of sulfate in the blood serum may often be accompanied by "normal" clearance of sulfate.

Thus, the present series includes 12 cases in which normal clearance values for sulfate were found in the cases of patients with increased amounts of inorganic sulfate in the serum. This seemingly contradictory situation had been observed previously by Macy and was partly responsible for the present investigation. It was subjected to a closer analysis by comparing the ratio of sulfate clearance to urea clearance in our original two groups of cases, namely, persons with normal and persons with increased concentrations of sulfate in the serum. For the former group (those with normal concentration of sulfate in the serum) the ratio of sulfate clearance to urea clearance averaged 0.65; for the latter group (those with increased concentration of sulfate in the serum) this figure was 0.85. The difference between these clearance ratios in our two groups is significant, as is shown by the analysis of our figures

summarized in table 3, and appears to be fundamentally related to all the seemingly contradictory data on sulfate excretion brought out by previous investigators as well as by the results of this study.

Excretion of Urea.—A survey of the various data pertaining to the excretion of urea in this same group of patients shows at once the similarity and the differences between the patterns of excretion of urea and of sulfate. The following facts may be noted. 1. In diffuse arteriolar disease with hypertension groups 1 and 2 (13 per cent) an increased concentration of blood urea was noted only infrequently. 2. In the presence of hypertension groups 3 and 4, more than half of the patients displayed an increased concentration of urea in the blood. 3. Only a small decrease of the percentage of those who had a urea clearance

TABLE 3.—*Comparison of the Ratio of Sulfate Clearance to Urea Clearance in Subjects with an Increased Concentration of Inorganic Sulfate in the Serum with the Ratio for Subjects with Normal Concentrations of Inorganic Sulfate in the Serum*

		Ratio of Sulfate Clearance to Urea Clearance	
	Number of Cases	Mean	Standard Deviation
Subjects with increased serum sulfate	24	0.85	0.36
Subjects with normal serum sulfate	26	0.65	0.24
	Difference = 0.20		
	S.D. of difference = 0.09		
$T = \frac{0.20}{0.09} = 2.22$			P = 0.03

T is used to test the significance of the difference between the means. P gives the probability of such a value of T occurring by chance (Fisher, R. A.: Statistical Methods for Research Workers, ed. 4, Edinburgh and London, Oliver and Boyd, 1932).

within normal limits was noted when the patients suffering from diffuse arteriolar disease with hypertension groups 1 and 2 were compared with those with hypertension groups 3 and 4. This comparative analysis definitely establishes the fact that in the more severe degrees of hypertension, as contrasted with milder forms, there is a far greater probability that either urea or sulfate will be retained in the blood than that decreases in the renal clearances of these two substances will be detected. 4. Retention of urea in the presence of a normal urea clearance is a rare finding. In only 1 (case 24) of the 50 cases studied was the urea clearance within normal limits when an actual accumulation of urea in the blood above normal limits had taken place. This is to be contrasted with the frequency with which the analogous situation is encountered with respect to sulfate, as was elaborated on earlier in this paper. A graphic analysis of many features of urea and sulfate excretion based on the patients investigated in this study is to be found in charts 1 and 2.

COMMENT

General Considerations.—If the state of renal excretory function as revealed by clearance tests prevailed for twenty-four hours a day, the results of those tests (for a given twenty-four hour level of excretion and assuming continuous production in the intermediary metabolism) should determine the amounts of any substance in the blood. Ingenious formulas have been devised to "translate" the work of excretion at

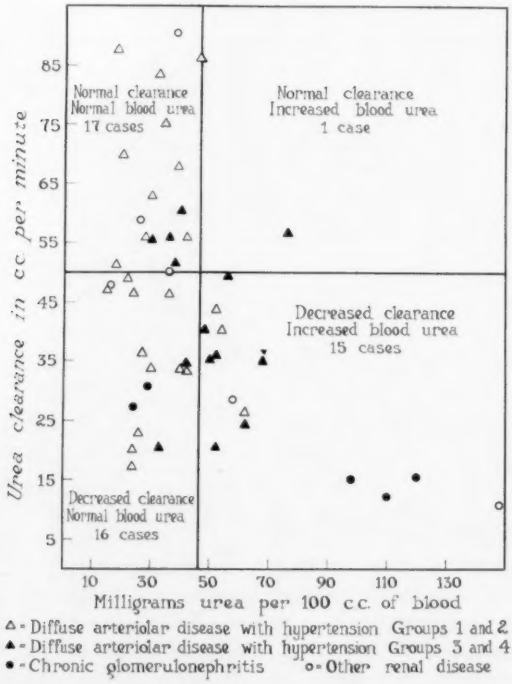

Chart 1.—Pattern of excretion of urea in patients with diffuse arteriolar disease with hypertension and renal disease. The horizontal line divides the "normal" (above) from the "decreased" range of clearances (below). The vertical line divides "normal" (left) from "increased" values in the blood and serum (right). Similarity of the manner in which urea and sulfate are eliminated in the group of patients studied is indicated by the similar frequency of the individual observations in the right lower and left upper and lower quadrants of this chart and of chart 2. The salient difference involves the frequency of combination of "increased" blood (serum) concentration with "normal" clearances represented in right upper quadrant. Whereas only 1 instance is observed in excretion of urea it is encountered 12 times in the pattern of excretion of inorganic sulfate.

lower urine volumes into "standard" clearances; but this should not make one forget that at the usually prevailing relatively low (that is, as compared to those existing under conditions of "maximal clearance") rates of excretion of urine reabsorption takes place much more than is ordinarily observed in clearance studies. Thus, for urea, Chesley [18] was able to show that below a critical lower level of urinary flow (0.35 cc. per minute) urea clearance is directly proportional to urine volume.

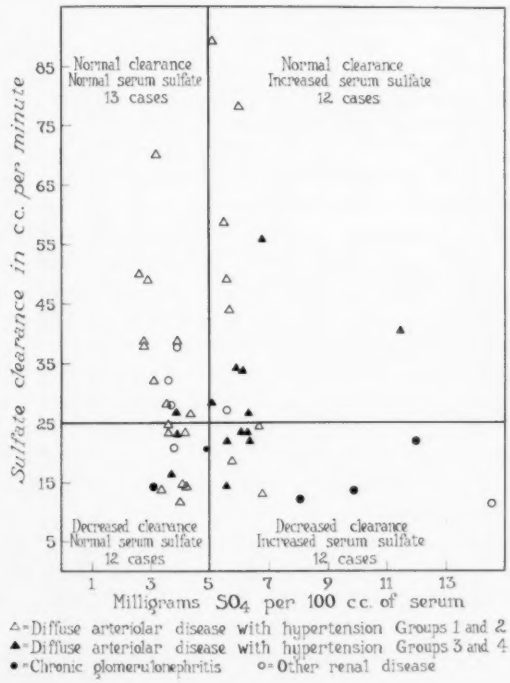

Chart 2.—Pattern of excretion of inorganic sulfate in patients with diffuse arteriolar disease with hypertension and renal disease. Note the comment in the legend for chart 1.

The observations by Hayman and Johnston and by Macy point to a continuously decreasing rate of excretion of inorganic sulfates with diminishing flow of urine. Thus, for practical purposes a given "clearance" does not rigidly imply such and such a concentration in the blood, a fact which is well illustrated by the considerable statistical

18. Chesley, L. C.: Urea Excretion at Low Urine Volumes: The Calculation of "Minimal" Urea Clearance, J. Clin. Investigation **17**:119-123 (March) 1938.

scattering in the well known figures of Van Slyke and his associates,[19] who plotted blood urea against urea clearance.

Serum Sulfate.—These considerations make it understandable that the concentration of a given waste product in the blood may have a significance which would not appear from the analysis of its rate of excretion under optimal circumstances of removal. Inorganic sulfate apparently is one of these substances. In addition to the importance of its retention in the blood, noted by other authors, its accumulation in 4 of every 5 cases of diffuse arteriolar disease with hypertension groups 3 and 4 (which comprise those cases in which there is a hypertensive vascular type of retinitis), as has been reported earlier in this paper, is striking. It appears worthy of note that, whereas in the two other clinical groups studied (table 2) the value for urea clearance is most likely to be indicative of renal damage, the value for concentration of serum sulfate is most likely to point to the diminished renal function in the group with hypertensive vascular retinitis.

This peculiar correlation definitely indicates the intimate relation between renal damage sufficient to bring about actual retention of an end product of normal protein metabolism and hypertensive vascular disease severe enough to be associated with retinitis in human beings. The assumption that arteriolar changes, whether due to an imbalance of physiologic forces, such as vasospasm, or to actual pathologic changes, carry a great deal of responsibility for both renal and retinal disturbances appears rather obvious in the light of present knowledge of the pathologic physiology of this disease.

Sulfate Clearance.—A review of the data submitted in table 1 indicates that "normal" and "decreased" values for sulfate clearance are equally distributed among the patients showing "normal" and "increased" concentrations of inorganic sulfate in the serum, practically one-half of the patients in each group having normal and one-half having diminished values for clearance of inorganic sulfate. This is clearly in contrast to the behavior of urea clearance in these two groups of patients, since the group with normal values for serum sulfate contained 58 per cent more patients with normal values for urea clearance than did the group with the values for serum sulfate above 5.0 mg. per hundred cubic centimeters.

The more detailed comparative analysis submitted earlier in this paper shows that the value for sulfate clearance as compared to that for urea clearance increases as inorganic sulfate in the blood accumulates above the normal concentration. In its turn, the value for urea clearance

19. Van Slyke, D. D.; McIntosh, J. F.; Möller, E.; Hannon, R. R., and Johnston, C.: Studies of Urea Excretion: VI. Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, J. Clin. Investigation **8**:357-374 (April) 1930.

does not maintain a constant ratio to the amount of "glomerular filtrate" as urea clearance becomes lower and lower with increased renal damage. Chasis and Smith [20] showed that the ratio of urea clearance to inulin clearance increases as urea clearance diminishes and that it approaches unity in the presence of the severest degree of renal insufficiency. This the authors stated to be due to the diminishing tubular reabsorption which goes hand in hand with the diminished concentrating power of the kidney. This approximation of the clearances with increasing urinary dilution can be reproduced in healthy dogs by submitting them to forced diuresis through intravenous administration of a solution of sodium sulfate, sucrose or urea (Shannon [21]).

Presumably the mechanism of excretion of sulfate, like that of excretion of urea, consists in ultrafiltration by the glomeruli followed by partial reabsorption by the tubules, with this difference, that the fraction of sulfate reabsorbed is greater than that of urea, since the value for sulfate clearance for practically all healthy persons is lower than that for urea. The potential capacity for reabsorption by the tubules of the healthy person, however, is much more limited for sulfate (Power, Goudsmit and Keith) than it is for urea.[22]

When the concentrating power of the kidney fails with advancing renal insufficiency, sulfate clearance as well as urea clearance tends to approach the level of inulin clearance. Thus, Keith, Power and

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20. Chasis, H., and Smith, H. W.: The Excretion of Urea in Normal Man and in Subjects with Glomerulonephritis, J. Clin. Investigation **17**:347-358 (May) 1938.

21. Shannon, J. A.: Urea Excretion in the Normal Dog During Forced Diuresis, Am. J. Physiol. **122**:782-787 (June) 1938.

22. The latter mechanism namely, the "unlimited" reabsorption of urea by the tubules, curiously enough, can be arrived at by inference only: the studies by T. Addis and D. R. Drury (The Rate of Urea Excretion: V. The Effect of Changes in Blood Urea Concentration on the Rate of Urea Excretion, J. Biol. Chem. **55**:105-111 [Feb.] 1923) and by Drury (The Rate of Urea Excretion: VI. The Effect of Very High Blood Urea Concentrations on the Rate of Urea Excretion, ibid. **55**:113-118 [Feb.] 1923) do not include data permitting one to calculate the extent of glomerular filtration; Shannon [21] suggestively indicated it to take place in dogs in that his experiments with urea given intravenously showed ratios of urea clearance to creatinine clearance essentially similar to some in which high urine flows were obtained by other means, but no data are presented indicating the concentration of urea in the blood reached in these experiments; and Goudsmit (The Renal Excretion of Inorganic Sulfates, Thesis, University of Minnesota Graduate School, 1939), on the basis of a limited number of experiments on dogs, was unable to recognize the concentration of urea (up to 100 mg. per one hundred cubic centimeters of plasma) as a factor determining its rate of excretion when this was compared with that of creatinine.

Peterson [23] reported approximately identical clearances of inorganic sulfate (5 cc.), urea (5 cc.) and sucrose (6 cc.) in a case of diffuse arteriolar disease with hypertension and severe renal insufficiency.[24] Generally speaking, the decrease of clearance of sulfate (in absolute numbers) would be less than that of urea, since the former starts at a lower level. Thus "endogenous" inorganic sulfate clearance numerically appears to undergo smaller changes than either urea clearance or inulin clearance when renal function goes from "100 per cent" down to low levels. Thus, as an index of glomerular filtration it would seem the least desirable of these three indexes of renal function.

Mechanism of Sulfate Retention.—The retention of sulfate in the body fluids, presupposing a normal metabolism of sulfur as such, theoretically can take place (1) through diminished glomerular filtration and (2) through increased tubular reabsorption.

1. In the group of cases in which the values for serum sulfate were within normal limits, 46 per cent of the patients showed urea clearances exceeding 50 cc. per minute, whereas of those with values for serum sulfate above 5.0 mg. per hundred cubic centimeters only 29 per cent had a normal value for urea clearance. Thus, in view of the established relation between urea clearance and the rate of glomerular filtration, it would appear that one of the factors responsible for the retention of sulfate in the body fluids is the diminution of glomerular filtration. Nevertheless, in a large number of cases the estimated magnitude of glomerular filtration appears sufficient for adequate elimination of inorganic sulfate, and thus tubular reabsorption would appear to be in part responsible for its retention. But the experimental data appear insufficient to incriminate an actual excess of tubular reabsorption for the retention of sulfates.

2. The only conditions that we are aware of at the present time in which increased tubular reabsorption may be active in causing sulfate retention are the toxemias of pregnancy. Anderson and Tompsett [25] found the inorganic sulfate content of serum to be normal in cases of normal pregnancy, but increases were observed in nearly all cases of eclampsia, even though the concentration of urea in the blood was still

23. Keith, N. M.; Power, M. H., and Peterson, R. D.: The Renal Excretion of Sucrose When Injected Intravenously in Man, Am. J. Physiol. **105**:60-61 (July) 1933.

24. These findings were presented at the meetings of the American Physiological Society at Cincinnati in 1933. They do not appear, however, in the printed abstracts published in the American Journal of Physiology.

25. Anderson, D. F., and Tompsett, S. L.: Observations on the Inorganic Sulphate Content of the Blood in Eclampsia, Brit. J. Exper. Path. **13**:130-132 (April) 1932.

normal. Similarly, Hunt and Wakefield [26] found the concentration of sulfate in the serum of 29 patients with preeclamptic toxemia to be increased in 22 (76 per cent); in none of these did the concentration of urea exceed 46 mg. per hundred cubic centimeters of blood. The possibility, therefore, would appear to exist (until either confirmed or refuted by future experimental evidence) that sulfate retention in these cases actually was due to the relatively increased tubular reabsorption.

The clinical picture of the toxemias of pregnancy is complicated. However, in many cases these conditions have definite features in common with diffuse arteriolar disease with hypertension groups 3 and 4. This, in turn, suggests that the retention of sulfate might be due in part, at least, to vascular disturbances.

Why Does Sulfate Tend to Accumulate in the Body Fluids Earlier than Does Urea?—The recent communication by Wakefield, Power and Keith (1939) presents data on a group of 651 persons whose renal function was subjected to various tests. Of this number, 22 per cent showed retention of urea, as compared with 30.4 per cent having an excess of sulfate in the serum. In addition, of all patients with increased values for blood urea, 79 per cent also had retention of sulfate, whereas of all patients with increased values for serum sulfate, only 57.1 per cent had retention of urea. These data prove beyond any doubt that, statistically speaking, there is retention of sulfate before there is retention of urea. Although the final explanation for this phenomenon will have to await further study of the comparative rates of excretion of each of these substances during twenty-four hour periods, we believe that the following tentative calculations may be helpful in explaining the difference between the patterns of excretion of these two end products of protein metabolism.

Normally, the ratio of nitrogen to sulfur in the urine varies between 13 and 16, averaging approximately 15. Since approximately 88 per cent of the sulfur excreted is in the form of inorganic sulfate and since urea is responsible for between 80 and 90 per cent of all nitrogen excreted, it may be stated tentatively that the ratio of urea nitrogen to inorganic sulfate sulfur in the urine should be not far from 15. In the blood at the upper limit of normal there is present $28/60 \times 46 = 21.5$ mg. urea nitrogen, and $32/96 \times 5.0 = 1.67$ mg. of inorganic sulfate sulfur, per hundred cubic centimeters of serum. Thus the ratio of urea nitrogen to sulfate sulfur in the blood equals 21.5/1.67, or approximately 13. Thus, in order to be able to excrete sulfate as readily as it does urea, the kidney would have to maintain a ratio of sulfate clearance

26. Hunt, A. B., and Wakefield, E. G.: Concentration of Serum Sulfate During Pregnancy and in Pre-Eclamptic Toxemia, Am. J. Obst. & Gynec. **38**: 498-501 (Sept.) 1939.

to urea clearance of 13/15, or 0.87. Normally, according to Keith, Power and Peterson,[27] this relation is approximately 0.50, and in our series, which, with a few exceptions, consists of cases of known renal or vascular disease, for all patients in whose cases a value for serum sulfate not exceeding 5 mg. per hundred cubic centimeters was noted the ratio of sulfate clearance to urea clearance amounted to 0.65. Since in order to prevent sulfate retention as efficiently as urea retention a ratio of 0.87 should be maintained, accumulation of sulfate before accumulation of urea is to be expected in a significant number of instances.

The Term "Renal Insufficiency."—Renal functional activity appears to be sufficient as long as the products that the kidney is supposed to eliminate do not accumulate in the body fluids above the highest acceptable limits of normal concentration. As soon as accumulation above such a concentration takes place, renal function appears insufficient, and renal insufficiency, etymologically speaking, is present. There appears to be a certain hesitancy of some authors in using this expression, and thus the word "azotemia" is frequently employed to indicate the presence of an increased amount of urea nitrogen or nonprotein nitrogen in the blood. Since sulfate in an appreciable number of instances does accumulate before urea does, "renal insufficiency" would appear the more inclusive expression and, while conveying the same idea, leaves room for the discovery of other non-nitrogenous materials accumulating in the blood in renal disease before there is an increase in the concentration of urea.

Clinical Interpretation of Increased Serum Sulfate.—It would seem worthy of a special analysis to attempt to ascertain whether the increase of the concentration of sulfate in the serum by itself has any particular clinical meaning. Thus, we thought it worth while to make a special study of those patients who showed normal values for blood urea, clearance and sulfate clearance and still had values for serum sulfate exceeding 5.0 mg. per hundred cubic centimeters. In the present series 5 instances of the kind were observed (cases 42, 3, 29, 49 and 47, table 4). We are able to report on the subsequent history of all of them: One patient (case 47) with diffuse arteriolar disease with hypertension group 4, or so-called malignant hypertension, was dead within three months; 1 other patient (case 49) died eleven months after his examination. Of the other 3 patients, 1 (case 42), at the end of the day in which the clearance test was performed, came down with bronchopneumonia; however, five days later, after the fever had subsided, the concentration of serum sulfate had returned to within normal limits (4.2 mg. per hundred cubic centimeters). This patient and the 2

27. Keith, N. M.; Power, M. H., and Peterson, R. D.: The Renal Excretion of Sucrose, Xylose, and Inorganic Sulphates in Normal Man: Comparison of Simultaneous Clearances, Am. J. Physiol. **108**:221-228 (April) 1934.

remaining ones were heard from between eight and sixteen months after the values for serum sulfate had been found to be elevated and were in a satisfactory condition. Thus, in the individual case no conclusions of prognostic significance can be drawn from the isolated finding of an increased concentration of inorganic sulfate in the serum.

Urea, sulfate, phosphate, creatinine, uric acid and many other more or less well defined compounds are among the products known to accumulate in the blood in the presence of failure of renal excretory function. Sometimes one appears to be retained much earlier than, or in considerable excess of, others. The clinician is aware that in the individual case the result of a single test does not adequately portray the finely differentiated picture of renal function. Thus, knowledge of the excretion of more than one substance, such as urea, is desirable, and the results of the present study appear to corroborate the findings of previous authors, indicating the definite usefulness of determination of the inorganic sulfate content of the serum.

TABLE 4.—*Retention of Sulfate as the Only Sign of Renal Insufficiency*

Case Number	Serum Sulfate, Mg. per 100 Cc.	Sulfate Clearance, Cc./Min.	Blood Urea, Mg. per 100 Cc.	Urea Clearance, Cc./Min.
42	6.0	78.0	34	75.0
3	5.7	43.8	39	67.6
29	5.6	49.0	20	69.6
49	5.5	58.0	46	86.4
47	5.1	28.2	40	60.3

SUMMARY AND CONCLUSIONS

Comparative studies of blood urea, urea clearance, serum sulfate and sulfate clearance were performed on 50 patients. The majority were suffering from diffuse arteriolar disease with hypertension of various degrees of severity, most of the remainder, from chronic glomerulonephritis and other diseases of the urinary tract. The selection of the patients was conducted in such a fashion that half of the group would have normal and the other half increased concentrations of sulfate in the serum.

The increased concentration of serum sulfate was found to occur in diffuse arteriolar disease with hypertension groups 3 and 4 in 4 of every 5 cases, the urea clearance, the value for blood urea and the sulfate clearance indicating renal damage with decreasing frequency. The correlation of renal damage sufficient to bring about actual retention of an end product of normal protein metabolism and hypertensive vascular disease severe enough to be associated with retinitis is significant. It is assumed that arteriolar disease may well be responsible for both the retinal and the renal changes.

Generally speaking, in the more severe degrees of hypertension, as contrasted with the milder forms, there is a far greater probability of retention of either urea or sulfate in the blood than of decreases in the renal clearance of these substances. In this respect the patterns of excretion of urea and of sulfate are essentially similar. However, whereas the association of retention of urea in the blood and a normal value for urea clearance was observed only in 1 instance, 12 instances were observed of increased serum sulfate in the presence of a normal value for sulfate clearance.

The increase of the concentration of serum sulfate itself is held responsible for this behavior, and an analogy is seen with observations on experimental animals as well as on human volunteers, in whom the intravenous injection of sodium sulfate leads to considerable increases in the value for sulfate clearance without significantly changing renal function otherwise. In accordance with the analogy drawn from these experimental observations, the ratio of sulfate clearance to urea clearance is significantly increased in the cases of those patients who have increased values for (endogenous) sulfate in the serum as compared to those with normal values for serum sulfate.

On the basis of the filtration-reabsorption theory the observations are discussed. A tentative explanation is offered of the fact that, statistically speaking, sulfate accumulates in the blood before there is retention of urea. Both diminished glomerular filtration and increased tubular reabsorption were taken into consideration as factors responsible for the sulfate retention. The latter mechanism may well play an important role in causation of the increased concentration of serum sulfate associated with the toxemias of pregnancy.

Thus, although conclusions of prognostic significance in renal disease should not be based on the value for serum sulfate any more than on any other single laboratory index, determination of this index is a valuable adjunct in appraising renal function, and the pattern of excretion of sulfate is of considerable interest to the student of renal and vascular disease.

PANCREATIC FUNCTION IN A CASE OF NONTROPICAL SPRUE

ALICE CHILDS, M.D.
AND
GEORGE F. DICK, M.D.
CHICAGO

There are only scattered references either to pancreatic function or to the use of pancreatic preparations in cases of nontropical or tropical sprue throughout the literature over a period of years. Among the early investigators of the enzyme test on external secretions of the pancreas in cases of sprue are Brown,[1] Ashford [2] and Castellani.[3] More recently, Sokhey and Malandkar [4] and Hernandez [5] have written on this subject. Snell [6] reported results in 1 of his cases. The results are conflicting, though the tests carried out according to more recently acceptable methods on "fasting duodenal contents" show normal or increased lipase activity, normal trypsin activity and normal or depressed amylase activity.

There is a great deal of criticism with regard to the methods used in this type of study and with regard to the value of these tests as an indication of actual pancreatic function. McClure and Jones [7] and Ivy [8]

From the Department of Medicine, University of Chicago Clinics.

1. Brown, T. R.: The Gastro-Intestinal Findings in a Case of Sprue with a Note on Treatment Based on These Findings, Bull. Johns Hopkins Hosp. **27**:289-291 (Oct.) 1916; The Absence of Pancreatic Secretion in Sprue and the Employment of Pancreatic Extract in the Treatment of the Disease, Am. J. M. Sc. **161**: 501-507 (April) 1921; A Note on the Administration of Pancreatic Extract in the Treatment of Sprue, J. Trop. Med. **24**:90 (April) 1921.

2. Ashford, B. K.: Certain Conditions of the Gastro-Intestinal Tract in Porto Rico and Their Relation to Tropical Sprue, Am. J. Trop. Med. **8**:507-538 (Nov.) 1928.

3. Castellani, A.: Beneficial Action of Raw Pancreas in Certain Cases of Sprue: Insulin in Cases of Sprue Complicated with Diabetes, J. Trop. Med. **28**: 230-231 (June) 1925; Brief Notes on the Administration of Liver, Pancreas and Stomach Extracts in Sprue, ibid. **33**:126 (May) 1930.

4. Sokhey, S. S., and Malandkar, M. A.: Pancreatic Function in Sprue, Indian J. M. Research **15**:921-933 (April) 1928.

5. Hernandez, L. G.: Pancreatic Juice in Normal Individuals and in Sprue, Porto Rico J. Pub. Health & Trop. Med. **6**:209-216 (Dec.) 1930.

6. Snell, A. M.: Clinical Observations on Nontropical Sprue, Arch. Int. Med. **57**:837-856 (May) 1936.

7. McClure, C. W., and Jones, C. M.: Studies in Pancreatic Function: The Enzyme Concentration of Duodenal Contents in Pathological Conditions Involving the Pancreas, Liver and Stomach, Boston M. & S. J. **187**:909-923 (Dec. 21) 1922.

8. Ivy, A. C.: Certain Aspects of Applied Physiology of External Pancreatic Secretion, Am. J. Digest. Dis. & Nutrition **3**:677-682 (Nov.) 1936.

have written excellent reviews covering the subject of pancreatic function and the physiology of the external pancreatic secretion. Ivy has brought out the point that because of dilution with bile, duodenal juice and gastric fluid, too much emphasis cannot be placed on concentration of enzymes obtained by duodenal drainage, but that it would be of great value to be able to estimate the total output of enzymes over a period of time. He expressed the hope that a dye may be discovered, eliminated exclusively by the pancreas, which can be used in a test for volume of secretion. At the time of his report, more than one hundred had been used unsuccessfully in his laboratory.

Quantitative analyses of stools with special emphasis on partition of fats, as well as determinations of the wet and dry weight and of the total amount of fat eliminated per day furnish additional information with regard to intestinal digestion and therefore with regard to pancreatic function. The type of curve obtained with the dextrose tolerance test may supply additional information in an investigation of the pancreas. In the use of pancreatic preparations most authors have relied on subjective improvement in their patients as a criterion for evaluating their results. Examples of this may be found in the works of Brown [1] and Castellani.[3] Silverman and his associates [9] used pancreatin and raw ground pancreas orally and investigated the enzymes in duodenal contents. Their results indicate that the digestive power of the duodenal contents is increased by administration of pancreatic preparations by mouth.

Morphologic studies in cases of nontropical and tropical sprue have not contributed anything definite toward a further understanding of the mechanism of this disease, nor have any specific pathologic changes in the pancreas been found to be associated with this disease. Suarez,[10] Fullerton and Innes,[11] Burgdorf and Barry,[12] Thaysen,[13] Anderson and Lyall,[14] Holst,[15] Jeckeln [16] and Rosenthal [17] all referred to autopsy

9. Silverman, D. N.; Denis, W., and Leche, S.: A Study of the Effect Produced on the Enzyme Concentration of the Duodenum by the Oral Administration of Certain Commercial Pancreatic Preparations, Am. J. M. Sc. **170**:727-730 (Nov.) 1925.

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studies in cases of sprue and reported no diagnostic morphologic lesions. Atrophic changes of the intestinal mucosa, decrease in weight of the viscera and decrease in subcutaneous fat are usually reported. Other changes in the intestines as described in some of these reports suggest that some associated pathologic condition, such as regional ileitis, may have been present. Whipple,[18] Blumgart,[19] Jarcho [20] and Reinhart and Wilson [21] described a clinical syndrome highly suggestive of sprue, associated with deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues and a relatively normal pancreas, and designated this by the term "intestinal lipodystrophy of Whipple."

A case of nontropical sprue is presented here in which the diagnosis was based on the findings to be described, which conform with the points for diagnosis brought out in the literature. Chronic recurring steatorrhea with bulky, foul-smelling stools, marked emaciation, glossitis, macrocytic anemia, multiple vitamin and mineral deficiencies, amenorrhea and nutritional edema were present. Further support for the diagnosis in the case reported here was obtained from roentgen evidence of edema of the jejunum, ileum and colon and from a flat dextrose tolerance curve. This syndrome is compatible with that described by Thaysen and Norgaard,[22] Manson-Bahr,[23] Castle and his associates,[24] Corr,[25] Fairley,[26] Snell,[6] Miller and Barker,[27] Moore and his associates,[28]

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(Footnotes continued on next page)

Bassett and his co-workers,[29] Brull and his associates,[30] Hanes and McBryde,[31] Bennett and his co-workers,[32] Linder and Harris,[33] Aub and his associates [34] and Mackie and Pound.[35]

We feel that more than the usual number of tests yielding information with regard to pancreatic function have been carried out in this case of nontropical sprue and that more than the usual clinical trial has been given pancreatic preparations. Therefore, a report of the case may be of interest.

REPORT OF A CASE

M. W., a 31 year old white woman, was admitted to the Billings Hospital on Oct. 29, 1937. She had had a gradual onset of symptoms three years previously, in the fall of 1934. At that time there had been a loss in weight of 34 pounds (15.4 Kg.), which she had failed to regain, a marked loss of appetite, increasing weakness and voluminous, foul, pale tan stools, occurring typically three to six times before 11 a. m. and accompanied with cramping pains in the lower part of the abdomen and gaseous distention. She voided frequently and had burning on urination, associated with dull pain in the lower part of the lumbar region. The menses decreased in amount of flow and occurred at irregular intervals. She consulted a number of physicians, but no diagnosis was established and no successful treatment instituted.

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In March 1935, after her marriage in January of that year, she again consulted a physician because of irregular menses, anorexia, excessive fatigue, frequency of urination and diarrhea. Her weight until late in 1934 had averaged 126 pounds (57.2 Kg.) but at this time was only 92 pounds (41.7 Kg.). Pulmonary tuberculosis, malignant tumor of the urinary bladder and amebiasis were considered by the physician. Roentgen examination of the chest, cystoscopic study, biopsy of material from the cervix, agglutination tests and examinations of the stool for parasites, pus and blood failed to establish any definite diagnosis. Laboratory examination revealed the value for hemoglobin to be 85 per cent. The erythrocytes numbered 4,400,000 and the leukocytes 9,600 per cubic millimeter of blood. The urinary sediment showed 15 to 20 leukocytes per high power field and many bacteria. The sputum was negative for tubercle bacilli.

The weight did not increase with a high caloric diet, and all the complaints were still present a year later, at which time she had not improved in any way, according to the physician's report.

For a year she had no medical supervision, and in March 1937 she appeared very anemic. The value for hemoglobin was 65 per cent. There were 2,750,000 erythrocytes and 6,700 leukocytes per cubic millimeter of blood. She first noticed a tendency to bruise easily about this time. She was treated with brewer's yeast and a preparation of liver (jeculin), as well as with intramuscular injections of iron, arsenic and phosphorus. At the end of April the value for hemoglobin was 70 per cent and the erythrocyte count 3,270,000 per cubic millimeter of blood. On May 2 she was given 500 cc. of whole blood by direct transfusion from a compatible donor. On May 8 the value for hemoglobin was 70 per cent and the erythrocyte count 3,380,000 per cubic millimeter. For two months after this the patient felt better, and the weight increased to 104 pounds (47.2 Kg.), although the diarrhea continued.

During hot weather, in July, the diarrhea became very severe, with liquid stools six to seven times daily, typically occurring before 11 a. m. In two weeks' time there was a loss of 12 pounds (5.4 Kg.), so that the weight was 92 pounds (41.7 Kg.), the lowest level reached since the initial loss of 34 pounds (15.4 Kg.). Edema of the ankles was first noticed with this exacerbation of severe diarrhea. The skin of the legs became tense and painful, and a scaling, itching, weeping rash appeared on the outer aspects of both legs and thighs. In August the patient noticed stiffness and tingling in the fingers and some tingling of the legs after defecation. After a cold in September a severe pain developed under both scapulas and was made worse by movements of the spine. On her own initiative, for a month before her appearance in the clinic she had taken Armour's liver extract by mouth, with a resulting definite increase in appetite. At no time had her diet been particularly limited except that in an endeavor to avoid "acid foods" for a year she had eaten no oranges, lemons or grapefruit. Her daily menus had included meat, potatoes, cooked and raw fruits and vegetables, apples or bananas between meals and an occasional glass of milk, of which she was not fond.

The patient had always lived in Chicago and had worked for the same wholesale grocery company for fifteen years. Prior to her admission to the hospital she had been unable to work for days at a time on several occasions. She had visited in Alabama twice since her marriage in 1935. The past and family histories added no significant information.

On her admission to the Billings Hospital physical examination revealed her to be pale and underweight. Her height was 65 inches (165 cm.). Her weight was 102 pounds (46.2 Kg.). The skin was dry. There were scaling lesions on the flexor aspect of the right arm, at the elbow and on the left side of the neck. On

TABLE 1.—*Laboratory Data Obtained at Weekly Intervals During First Period of Hospitalization* *

		Stool Analyses								Dextrose Tolerance			Blood Chemistry							Hematologic Studies					Therapy			
						Fat Partition																					
Week of	Body Weight, Kg.	Daily Wet Stool, Gm.	Daily Dry Stool, Gm.	Daily Fat Elimination, Gm.	Fat, % Dry Weight	Fatty Acids, %	Soap, %	Neutral Fats, %	Fasting Level, Mg./100 Cc.	Maximum Rise, Mg./100 Cc.	Vehicle	Method of Administration	Plasma Proteins, Gm./100 Cc.	Ca, Mg./100 Cc.	P, Mg./100 Cc.	Chlorides, mM/L	pH	CO_2, mM/L	Cholesterol, Mg./100 Cc.	Hemoglobin	Red Blood Cells	Reticulocytes	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Cell Volume	Pancreatic Preparations	Vitamins	Liver Extract	Minerals
10/29/37	42.3	1194	104.0	60.8	58.1	72.6	18.2	9.2	72	18	H_2O	Oral	4.96	6.6	5.5	...	...	....	86	9.4	2.90	...	...	....	..	.....	.....	.....	.....
11/ 5/37	40.3	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	109	7.5	23.1	...	12.0	2.87	...	101	41.8	29	.....	.....	.....	.....
11/12/37	41.1	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	10.7	2.73	...	...	....	..	Pancreatic juice	.....	.....	.....
11/19/37	42.2	751	81.7	36.6	45.1	81.6	7.6	10.8	95	6	H_2O	Oral	5.28	7.2	3.0	104	7.4	23.3	...	12.5	3.26	0.1	...	....	..	Pancreatic juice	.....	.....	.....
11/26/37	41.4	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	12.0	3.22	1.7	...	....	..	Pancreatic juice	.....	.....	.....
12/ 3/37	41.4	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	12.5	3.67	2.2	...	....	..	Pancreatic juice	.....	.....	.....
12/10/37	41.8	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....
12/17/37	42.2	735	82.2	26.5	32.3	69.3	5.5	25.2	..	..	.....	.....	....	...	...	...	...	....	...	13.0	3.72	...	...	....	..	.....	.....	.....	.....
12/24/37	41.4	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....
12/31/37	44.6	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....
1/ 7/38	43.9	554	91.0	32.4	35.6	71.2	11.1	17.7	102	19	H_2O	Oral	5.51	8.6	3.5	...	...	....	...	10.8	3.15	2.4	...	....	..	.....	.....	.....	.....
1/14/38	44.6	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....
1/21/38	45.6	556	92.6	39.6	42.8	77.6	7.2	15.2	..	..	.....	.....	....	...	...	...	...	....	...	11.0	3.81	1.2	...	....	..	.....	.....	.....	.....
1/28/38	47.5	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	11.2	3.90	1.2	...	....	..	Pancreatic juice	.....	.....	.....
2/ 4/38	48.2	...	....	....	....	....	....	....	..	..	.....	.....	....	7.0	4.3	...	...	....	...	11.9	3.46	0.9	...	....	..	Pancreatic juice	.....	.....	.....
2/11/38	49.0	...	....	....	....	....	....	....	92	16	H_2O	Oral	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....
2/18/38	47.3	489	87.0	36.8	42.3	79.5	8.2	12.3	96	40	Pancreatic juice	Duodenal tube	5.94	...	...	...	...	....	135	12.0	4.11	2.0	90	29.2	37	.....	.....	.....	.....
2/25/38	47.3	...	....	....	....	....	....	....	97	63	Pancreatic juice	Duodenal tube	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....
3/ 4/38	48.7	...	....	....	....	....	....	....	88	41	H_2O	Duodenal tube	....	...	...	...	...	....	...	....	....	...	...	....	..	.....	.....	.....	.....

* The patient was on a constant diet of 150 Gm. of carbohydrate, 85 Gm. of protein and 141 Gm. of fat.

both legs and the outer aspects of the thighs were weeping, bleeding, scaling lesions with tense pitting edema of both legs extending from the ankles to the knees but not involving the feet. There were some carious teeth. There were a few aphthous lesions on the tongue and on the buccal mucosa. The tonsils were enlarged and cryptic. The blood pressure was 78 systolic and 54 diastolic, with tingling and stiffness of the fingers after application of the sphygmomanometer cuff for less than one minute. The lower portion of the abdomen was greatly distended. There was no rigidity. No masses were observed. Tenderness and rigidity on motion were elicited over the lower dorsal segments of the spine. Clubbing of the fingers and toes was observed. Examination otherwise gave essentially negative results.

During the first stay in the hospital, from Oct. 29, 1937 to March 4, 1938, the patient was maintained on a diet of 150 Gm. of carbohydrate, 85 Gm. of protein, and 141 Gm. of fat (table 1). Immediately prior to the quantitative collection of two day specimens of stool, a constant research diet of the same value was given the patient. Her weight increased 6.4 Kg. during this stay in the hospital, after an initial loss of 2 Kg. at the time when the edema of the extremities disappeared. Analyses of the dry stools by the method of Bloor [36] were carried out by Dr. H. A.

TABLE 2.—*Enzyme Determinations on Duodenal Contents with the Patient Fasting*

	Time of Lipase Action	Time of Trypsin Action	Gm. of Maltose Converted by Amylase
11/16/37			
Without stimulation	Less than 2¼ min.	12½ min.	0.25
With stimulation	Less than 2 min.	4½ min.	0.18
1/27/38			
Without stimulation	1 min. 40 sec.	7 min.	0.55
1st specimen after stimulation	10 sec.	4½ min.	0.57
2d specimen after stimulation	25 sec.	3 min.	0.56

Trangsrud before, during and after administration of 500 cc. of pancreatic juice daily by duodenal tube, divided into three doses and given one-half hour after meals. The pancreatic juice was provided through the courtesy of Dr. Lester Dragstedt of the department of surgery of the University of Chicago and was obtained from dogs with pancreatic fistulas prepared by his method.[37] The stools decreased in number and weight during the whole stay in the hospital but the diminution was most marked in the periods of administration of pancreatic juice. Immediately before the pancreatic juice was given in both instances, enzyme determinations (table 2) were carried out on "fasting duodenal contents" by the method of Lueders [38] as modified by Hollander.[39] In each of the two tests the activity of lipase was increased and that of trypsin and amylase was normal.

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The daily elimination of fat in the stools showed a definite decrease but remained higher than the normal average of 10 per cent to 25 per cent of the dry weight in twenty-four hours. The maximum decrease occurred after administration of pancreatic juice. The partition of fats remained relatively constant in all determinations, the level of fatty acids and that of soaps being higher than the normal average of 32 per cent and 26 per cent respectively and the neutral fraction being below the normal average of 42 per cent.

Flat dextrose tolerance curves were obtained in all tests in which dextrose was administered orally. A rise of 40 mg. and more per hundred cubic centimeters was obtained when the dextrose was placed directly in the duodenum by tube, whether the vehicle was pancreatic juice or water.

The blood pressure averaged between 70 and 80 systolic and 50 to 55 diastolic throughout this period of observation. A Trousseau sign could be elicited at any time after the tourniquet or blood pressure cuff was in use for more than a minute, and the patient always walked stiffly and complained of numbness and tingling in the hands and feet. Without specific calcium therapy the calcium values rose slowly over a period of weeks from 6.6 mg. to 8.6 mg. per hundred cubic centimeters, without definite change in the mild symptoms of tetany mentioned. All determinations of the level of phosphorus gave normal values, varying from 3.0 to 5.5 mg. per hundred cubic centimeters. The plasma proteins were at edema level of 4.96 Gm. per hundred cubic centimeters on admission and did not exceed 5.94 Gm. per hundred cubic centimeters at any time. The values for blood cholesterol were low on admission and rose to low normal values at the time of discharge.

Slight reticulocyte response occurred while pancreatic juice was being used. The values for hemoglobin did not exceed 13 Gm. per hundred cubic centimeters, but the erythrocyte count rose steadily from a "low" of 2,730,000 to 4,110,000 per cubic millimeter. The mean corpuscular volume decreased from 101 microns to 90 microns and the value for mean corpuscular hemoglobin from 41.8 to 29.2, while the cell volume per cent increased from 29 to 37.

Culture of the stool was negative for Monilia after eleven days. Gastric analysis with an Ewald test meal gave normal results. The urea clearance was normal. Tests of hepatic function with bromsulfalein and galactose revealed no abnormality. The icterus index was 13. A fat tolerance test when the testing material was given either in water or in pancreatic juice yielded a flat curve. The biophotometric test showed normal light adaptation. The test for parathyroid hyperfunction gave a rise of 0.5 millimols per liter in rabbit serum, which is equivalent to a positive reaction, indicating normal function.

Proctoscopic examination revealed no abnormality. The basal metabolic rate varied from $+2$ per cent to -17 per cent. Roentgen examination showed no evidence of pancreatic stone or of osteoporosis, a normal esophagus, stomach and duodenal bulb and diffuse edema of the mucosa of the jejunum, the terminal portion of the ileum and the colon, associated with diffuse dilatation of the colon. An electrocardiographic tracing showed evidence of myocardial damage.

There was one elevation of temperature to 101 F. for three to four days, during which time the urine was loaded with leukocytes and on culture yielded Bacillus coli. The urine became normal after administration of sulfanilamide, 1 Gm. daily for two days, followed by ammonium chloride, 1.2 Gm. daily for two weeks, and mandelic acid, 16 cc. for ten days.

The patient was discharged from the hospital with no medication and instructed to eat a general diet without limitation. She gained weight at home, but the

stools became more frequent and were accompanied by some abdominal cramps and distention. After two weeks at home the patient complained of increasing numbness and tingling in the hands and feet, with loss of appetite and generalized weakness. A week later (March 24) she was readmitted to the hospital because of continued numbness and tingling of the extremities and loss of the voice after drinking cold water (table 3).

There had been a gain of 3 Kg. during this interval, but the hemoglobin level had decreased almost 2 Gm. to an admission value of 10.3 Gm., while the erythrocytes numbered 3,840,000 per cubic millimeter. The value for plasma proteins was 6.18 Gm., that for calcium 6.22 mg. and that for phosphorus 2.8 mg. per hundred cubic centimeters. There was a further drop in calcium to 5.86 mg. per hundred cubic centimeters. For three weeks the patient was given vitamin B complex in the form of 45 Gm. of vegex (an autolyzed yeast extract) daily. The reticulocytes did not exceed 0.2 per cent, and the hemoglobin dropped to a low of 9.8 Gm. Liver extract was then given intramuscularly in the form of Lederle's concentrate, 1 cc. daily for seventeen days. The reticulocytes rose to 4.2 per cent, the value for hemoglobin to 12.2 Gm. and the erythrocyte count to 4,050,000 per cubic millimeter. Lilly's liver extract, 3 cc. intramuscularly daily for three weeks, was used, during which time the reticulocytes did not exceed 2.2 per cent, and the concentration of hemoglobin was no more than 12 Gm., while the erythrocyte count rose to 4,270,000 per cubic millimeter. The patient regained her appetite; her weight increased another 2.5 Kg. during this time, and the value for calcium rose to 8.4 mg. per hundred cubic centimeters. The patient menstruated for the first time in more than a year.

Elimination of fat in the stools increased from a daily output of 24.3 Gm. just preceding the use of liver to 57 Gm. per twenty-four hours after more than five weeks of daily injections of liver. At the time at which injections of liver extract were reduced to weekly intervals, 0.8 Gm. of ferrous sulfate was given by mouth daily. At the time of discharge from the hospital the patient's blood pressure remained low, the systolic level being not above 80 and the diastolic no higher than 60. The electrocardiogram showed no further change. The appetite was excellent; the stools were semiformed, occurring once to twice daily; the body weight on discharge was 51.4 Kg. The patient moved about much less stiffly than at the time of admission. She was sent home to observe the following regimen: a diet of approximately 150 Gm. of carbohydrate, 85 Gm. of protein and 141 Gm. of fat; three capsules containing vitamins A, B and D daily; 75 mg. of vitamin C daily; 3.6 Gm. of vitamin B as brewer's yeast daily; 3 Gm. of calcium gluconate daily, and 0.2 Gm. of ferrous sulfate daily. She was to return to the clinic at weekly intervals to receive intramuscular injections of 1 cc. of Lederle's liver extract concentrate.

During an eight month interval in the clinic the patient maintained her weight well, had alternate periods of formed stools and watery diarrhea and complained of loss of appetite during hot weather. Administration of pancreatic substance (Armour's pancreatin), 4 Gm. daily, was started on August 21, after which the appetite improved. During October and November liver was given twice a week because of continued intervals of diarrhea and abdominal cramps. Use of pancreatic substance was discontinued on December 12, because it was unobtainable until December 21, when its administration was resumed at the previous level of dosage. The patient lost her appetite within three days of the time pancreatic substance was discontinued and regained it almost immediately after the preparation was given again. In anticipation of rehospitalization, administration of liver

TABLE 3.—*Laboratory Data Obtained at Weekly Intervals During Second Period of Hospitalization* *

		Stool Analyses							Dextrose Tolerance				Blood Chemistry							Hematologic Studies						Therapy		
						Fat Partition																						
Week of	Body Weight, Kg.	Daily Wet Stool, Gm.	Daily Dry Stool, Gm.	Daily Fat Elimination, Gm.	Fat, % Dry Weight	Fatty Acids, %	Soap, %	Neutral Fats, %	Fasting Level, Mg./100 Cc.	Maximum Rise, Mg./100 Cc.	Vehicle	Method of Administration	Plasma Proteins, Gm./100 Cc.	Ca, Mg./100 Cc.	P, Mg./100 Cc.	Chlorides, mM/L	p_H	CO_2, mM/L	Cholesterol, Mg./100 Cc.	Hemoglobin	Red Blood Cells	Reticulocytes	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Cell Volume	Pancreatic Preparations	Vitamins	Liver Extract	Minerals
3/24/38	51.8	...	....	....	....	....	....	....	97	46	H_2O	Duodenal tube	6.18	6.2	2.8	...	...	....	...	10.3	3.84	...	....	....	..	.....	.....	.....	.....
3/31/38	50.4	...	....	....	....	....	....	....	97	75	Pancreatic juice	Duodenal tube	....	5.9	3.8	...	...	....	...	12.0	3.92	0.3	....	....	..	.....	Vegex	.....	.....
4/ 7/38	51.3	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	10.0	3.78	...	....	....	..	.....	Vegex	.....	.....
4/14/38	52.9	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	9.9	3.79	...	....	....	..	.....	Vegex	.....	.....
4/21/38	51.5	314	54.1	24.3	44.7	76.9	6.7	16.4	..	..	.....	.....	....	...	...	...	...	....	...	9.8	3.87	0.2	....	....	..	.....	Vegex	.....	.....
4/28/38	52.6	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	11.7	3.86	2.2	....	....	..	.....	.....	1 cc. concentrated	.....
5/ 5/38	51.7	...	....	....	....	....	....	....	..	..	.....	.....	....	6.9	4.1	...	...	....	...	12.2	4.05	4.2	....	....	..	.....	.....	1 cc. concentrated	.....
5/12/38	52.7	...	....	....	....	....	....	....	..	..	.....	.....	6.46	...	...	...	...	....	141	11.9	4.02	2.0	....	....	..	.....	.....	3 cc. concentrated	.....
5/19/38	52.0	412	63.1	28.4	45.7	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	12.0	4.27	2.2	....	....	..	.....	.....	3 cc.	.....
5/26/38	53.3	...	....	....	....	....	....	....	88	18	H_2O	Oral	....	...	...	...	...	....	...	11.8	4.25	1.0	....	....	..	.....	.....	3 cc.	.....
6/ 2/38	52.5	687	115.4	57.0	49.3	54.8	30.2	15.0	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	....	....	..	.....	.....	3 cc.	.....
6/ 9/38	51.9	...	....	....	....	....	....	....	..	..	.....	.....	6.26	8.4	4.3	110	7.38	24.0	122	12.5	4.54	...	....	....	..	.....	.....	.....	0.8 Gm. $FeSO_4$
6/16/38	51.4	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	....	....	..	.....	ABD C B complex	3 cc.	0.8 Gm. $FeSO_4$

*The patient was on a constant diet of 150 Gm. of carbohydrate, 85 Gm. of protein and 141 Gm. of fat.

TABLE 4.—*Laboratory Data Obtained at Weekly Intervals During Third Period of Hospitalization* *

TABLE 4.—*Laboratory Data Obtained at Weekly Intervals During Third Period of Hospitalization* *

Week of	Body Weight, Kg.	Stool Analyses: Daily Wet Stool, Gm.	Daily Dry Stool, Gm.	Daily Fat Elimination, Gm.	Fat, % Dry Weight	Fat Partition: Fatty Acids, %	Soap, %	Neutral Fats, %	Dextrose Tolerance: Fasting Level, Mg./100 Cc.	Maximum Rise, Mg./100 Cc.	Vehicle	Method of Administration	Blood Chemistry: Plasma Proteins, Gm./100 Cc.	Ca, Mg./100 Cc.	P, Mg./100 Cc.	Chlorides, mM/L	pH	CO_2, mM/L	Cholesterol, Mg./100 Cc.	Hematologic Studies: Hemoglobin	Red Blood Cells	Reticulocytes	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Cell Volume	Therapy: Pancreatic Preparations	Vitamins	Liver Extract	Minerals
2/16/39	47.7	...	....	....	....	....	....	....	78	5	H_2O	Oral	5.54	6.8	1.9	106	7.32	21.0	98	10.5	3.10	2.0	....	....	..	.....	B1, C, D	Oral, 45 cc.	Cu, Fe
2/23/39	45.6	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	10.0	3.60	1.6	....	....	..	.....	B1, C, D	Oral, 45 cc.	Fe, Ca
3/ 2/39	47.4	736	91.2	53.5	58.6	67.2	15.0	17.7	..	..	.....	.....	....	6.9	3.3	...	...	....	...	9.2	3.10	2.8	....	....	..	.....	B1	Oral, 45 cc.	Fe, Ca
3/ 9/39	46.4	.. .	....	....	....	....	....	....	..	..	.....	.....	5.75	6.6	1.3	101	...	....	160	8.9	2.60	5.0	99.3	29.4	31	.....	B1, C	Oral, 60 cc.	Fe, Ca
3/16/39	44.5	...	....	....	....	....	....	....	..	..	.....	.....	....	6.6	2.1	...	...	....	...	9.0	2.90	10.2	....	....	..	Commercial	.....	1M., 3 cc.	.....
3/23/39	46.7	...	....	....	....	....	....	....	..	..	.....	.....	....	6.1	1.5	...	...	....	...	9.5	3.40	3.6	....	....	..	Commercial	B1, C, D	1M, 3 cc.	Ca, Fe
3/30/39	47.0	...	....	....	....	....	....	....	..	..	.....	.....	....	6.5	1.5	...	...	....	...	9.4	3.30	2.3	....	....	..	Broiled	C, D	1M, 3 cc.	Fe, Ca
4/ 6/39	47.6	...	....	....	....	....	....	....	..	..	.....	.....	....	5.7	2.5	...	...	....	...	9.1	3.47	3.0	....	....	..	Broiled	B1, D	1M, 3 cc.	Fe, Ca
4/13/39	48.8	...	....	....	....	....	....	....	86	14	H_2O	Oral	5.34	6.6	2.5	...	...	....	...	10.0	3.70	4.5	....	....	..	.....	B1, D	.....	Fe, Ca
4/20/39	47.8	...	....	....	....	....	....	....	92	16	After cortin (15 cc. IM)		4.98	6.6	2.7	111	...	....	...	11.0	3.90	0.8	80.1	27.5	32	Raw pulp	B1	3 cc. IM, concentrated	Fe, Ca
4/27/39	46.7	...	....	....	....	....	....	....	84	23	H_2O	Oral	5.95	7.5	2.6	...	...	....	...	....	....	...	....	....	..	.....	B1, D	3 cc. IM, concentrated	Fe, Ca
5/ 4/39	44.5	...	....	....	....	....	....	....	..	..	.....	.....	....	7.2	3.1	...	...	....	...	....	....	...	....	....	..	.....	B1, D	3 cc. IM, concentrated	Fe, Ca
5/11/39	46.1	418.6	79.5	40.7	51.2	47.4	35.4	17.2	..	..	.....	.....	5.57	7.2	2.6	...	...	....	123	11.0	3.50	...	....	....	..	.....	B1, D	3 cc. IM, concentrated	Fe, Ca
5/18/39	45.7	238.3	53.4	28.8	54.0	47.0	39.2	13.8	..	..	.....	.....	....	7.5	3.0	...	...	....	...	....	....	...	....	....	..	.....	B1, D	3 cc. IM, concentrated	Fe, Ca
5/25/39	46.0	363.8	73.5	36.0	49.0	51.2	34.0	14.8	..	..	.....	.....	....	...	...	...	...	....	...	....	....	...	....	....	..	.....	B1, D	3 cc. IM, concentrated	Fe, Ca
6/ 1/39	46.5	...	....	....	....	....	....	....	..	..	.....	.....	4.96	7.3	3.2	...	...	....	...	....	....	...	....	....	..	.....	B2, D	3 cc. IM, concentrated	Fe, Ca
6/ 8/39	47.5	...	....	....	....	....	....	....	..	..	.....	.....	....	...	...	...	...	....	...	12.0	3.97	1.0	....	....	..	Commercial	B1, B2, D	Once in 4 days	Fe, Ca
6/15/39	48.2	...	....	....	....	....	....	....	83	38	H_2O	Oral	5.16	6.5	3.4	...	...	....	...	....	....	...	....	....	..	Commercial	B1, B2, D	Once a week	Fe, Ca

* From 2/18 to 5/10 the patient was on a constant diet of 150 Gm. of carbohydrate, 78 Gm. of protein and 100 Gm. of fat. From 5/11 to 6/20 she was on a constant diet of 155 Gm. of carbohydrate, 175 Gm. of protein and 92 Gm. of fat.

extract was discontinued on Jan. 7, 1939, and owing to an unavoidable delay the patient was not admitted to the hospital until February 16. By February 8 she had glossitis and was passing small, loose stools three to four times daily, with much abdominal distention. She had frequent nosebleeds and a number of subcutaneous ecchymoses.

On admission to the hospital (February 16) the patient weighed 47.7 Kg. The value for hemoglobin was 10.5 Gm. The erythrocyte count was 3,100,000 per cubic millimeter, with 2 per cent reticulocytes. The value for plasma proteins was 5.54 Gm., that for calcium 6.8 mg., that for phosphorus 1.9 mg. and that for cholesterol 98 mg. per hundred cubic centimeters of blood. Urinary excretion of ascorbic acid after administration of 480 mg. of ascorbic acid intravenously was within normal limits. The patient was given 45 cc. of a concentrated preparation of liver extract orally, vitamin C in 1,000 mg. doses orally, vitamin B_1 intramuscularly, 30 cc. of crude cod liver oil orally and 6 mg. of calcium gluconate by mouth, all daily. She had acute abdominal distress with marked abdominal distention and rigidity, frequent loose stools and painful subcutaneous hematomas around the elbows and in the groins. The concentration of hemoglobin dropped to 8.9 Gm. The erythrocyte count was 2,600,000 per cubic millimeter. The mean corpuscular volume was 99.3; the mean corpuscular hemoglobin, 29.4; the bleeding time, two minutes; the clotting time, five minutes and the platelet count, 210,000. A quantitative analysis of the stool at this time by the Fowweather modification [40] of the Saxon method [41] showed daily elimination of 53.5 Gm. of fat. All medication by mouth was discontinued on March 9, and within a few days the patient's general condition improved. The hemorrhagic manifestations disappeared; the abdomen became soft, and the stools became semiformed and less frequent.

The greatest reticulocytic rise obtained at any time occurred during the next few days, the value reaching of 10.2 per per cent. Daily intramuscular liver therapy, 3 cc. of Chappel's concentrate (this was changed to 3 cc. of Lederle's concentrate daily on April 20) was resumed on March 10 and continued throughout the stay in the hospital. By April 20 the concentration of the hemoglobin had reached 11 Gm.; the erythrocyte count was 3,900,000 per cubic millimeter, with 0.8 per cent reticulocytes. The mean corpuscular volume was 80; the mean corpuscular hemoglobin, 27.5. Armour's pancreatic substance was given for a few days, and then its use was discontinued while fresh broiled whole pancreas, 200 Gm. daily, was given for three weeks. The patient was unable to tolerate this diet, and so it was discontinued. Raw beef pancreas reduced to a pulp (100 cc.) was given by duodenal tube for four days. The patient complained of loose stools and abdominal distress and was unable to tolerate this preparation.

Because of interest in Verzar's discussion of the relation of the adrenal cortex to intestinal absorption,[42] dextrose tolerance determinations were made on three consecutive days, the second test being carried out after 15 cc. of extract of adrenal cortex was given intramuscularly. There was no significant difference in the maximum rise in the level of blood sugar in the three tests. On the day after administration of adrenal cortex extract the blood pressure reading was the highest ever obtained, being 110 systolic and 65 diastolic.

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40. Fowweather, F. S.: The Determination of the Amount and the Composition of the Fat of Feces: I. Investigation of a "Wet" Method and Comparison with the "Dry" Method, Brit. J. Exper. Path. **7**:7-14 (Feb.) 1926.

41. Saxon, G. J.: A Method for the Determination of the Total Fats of Undried Feces and Other Moist Masses, J. Biol. Chem. **17**:99-102, 1914.

42. Verzar, F.: The Adrenal Cortex and Intestinal Absorption, Am. J. Digest. Dis. & Nutrition **4**:545-546 (Nov.) 1937.

Calcium and iron by mouth were given again, beginning on March 23, and vitamin D in the form of drisdol (crystalline vitamin D in propylene glycol) (20 drops, or 5,000 U. S. P. units of vitamin D) was given daily by mouth. Administration of these minerals and this vitamin D preparation was continued throughout the rest of the stay in the hospital.

The diet, which had approximate values of 150 Gm. of carbohydrate, 78 Gm. of protein and 100 Gm. of fat, was changed to a high protein diet of 155 Gm. of carbohydrate, 175 Gm. of protein and 92 Gm. of fat on May 11. The stools decreased in bulk, while the daily elimination of fat averaged 50 per cent of the dry weight, as determined by the wet method.

At the time of discharge the patient weighed 48.2 Kg. The value for calcium was 6.5 mg., that for phosphorus 3.4 mg., that for hemoglobin 12 Gm. The erythrocyte count was 3,970,000 per cubic millimeter, with 1 per cent reticulocytes. The patient was taught to weigh her own diet of 200 Gm. of carbohydrate, 175 Gm. of protein and 90 Gm. of fat. The following daily medication was prescribed: calcium gluconate, 4 Gm.; ferrous sulfate, 1.6 Gm.; drisdol (crystalline vitamin D in propylene glycol), 20 drops; pancreatin, 4 Gm., and nicotinic acid, 10 mg. She returned to the clinic at weekly intervals to receive 3 cc. of Lederle's liver extract concentrate and 50 mg. of vitamin B_1 intramuscularly.

The treatment has continued as outlined until the present time. The patient's weight has averaged 48 Kg., the value for hemoglobin has varied from 11.4 to 12 Gm. and that for blood calcium from 5.8 to 8.8 mg. per hundred cubic centimeters. When she has had acute infections of the upper respiratory tract, none of which has been severe, she has lost as much as 10 pounds (4.5 Kg.) in a week, but on recovery from the cold has regained that weight within two weeks. The stools become more frequent during these infections but of no greater volume. The patient has increased her activities greatly and is conscious of a sense of well-being which she had not experienced previously.

COMMENT

The greatest improvement in the condition of this patient occurred during the first period of hospitalization, when the therapy consisted only of administration of a constant diet with a fairly high fat content and of pancreatic juice. The stools decreased in daily wet and dry weight, in the per cent of fat present in the dry weight and in the total weight of the fat eliminated daily. The fact that the pancreatic juice brought about a more definite decrease than did liver extract alone is evidence that some factor of value in intestinal digestion, present in normal pancreatic juice, was deficient in this case. The partition of fat, with low values for neutral fat and high values for soaps and free fatty acids, is evidence of adequate fat splitting and poor absorption. Further evidence of normal pancreatic function is furnished by the values for nitrogen in the dry stool, which never exceeded 3.5 Gm. daily, and by the results obtained from tests of "fasting duodenal content" on the mornings before the periods of administering pancreatic juice were started, in which values for proteolytic and amylolytic enzymes were normal and lipolytic activity was increased. These findings suggest that in this typical case of nontropical sprue there existed a deficiency in some pancreatic factor as yet undemonstrated. Similar results were

obtained by Trangsrud[43] in a study on totally depancreatized and totally depancreatized dogs with ligated ducts fed large quantities of pancreatic juice.

In addition to the objective findings listed, the greatest subjective improvement occurred during the first period of hospitalization, after the use of pancreatic juice at a time when the stools were well formed and were passed at eighteen hour intervals. No comparable sense of well-being was experienced until the end of the third period of hospitalization, at which time the patient had been taking a high protein diet, a commercial pancreatic preparation, 3 cc. of a liver preparation at weekly intervals, calcium and iron by mouth and vitamin B, D and C concentrates. The high protein diet was well tolerated by the patient and, in fact, conformed to her own tastes more satisfactorily than any other diet attempted. This diet is a possible factor both in stimulating external pancreatic secretion and in utilization of the liver extract.

With the use of dried pancreatic substance (Armour's pancreatin) an increase in appetite occurred, and when the preparation was discontinued for an interval anorexia appeared. The appetite was regained when use of the preparation was resumed. Pancreatic juice, which produced objective and subjective improvement, was not obtainable after the first period of hospitalization. On the other hand, raw pancreas in pulp form was not well tolerated, though given by duodenal tube.

When the dextrose used in the dextrose tolerance test was administered by duodenal tube with pancreatic juice as the vehicle instead of orally with water as the vehicle, it was at first thought that further proof of the value of pancreatic preparations had been obtained, because the maximum rise of the level of dextrose was 40 mg. per hundred cubic centimeters, or more. These were the first normal values obtained. On repetition of the test, however, equal elevations resulted when the dextrose was given in water by duodenal tube. All subsequent tests in which the dextrose was given by mouth in water resulted in the usual flat curves.

The low values for blood calcium accompanied by normal or low values for inorganic phosphorus speak against hypoparathyroidism and appear to have been the result of high calcium excretion in the form of soaps in the stool or possibly of faulty intestinal absorption and increased rate of elimination of fecal material due to the diarrhea. The absence of active tetany may have been the result of the low levels of plasma protein and therefore of a decreased proportion of un-ionized calcium leaving ionized calcium values above the level of tetany. Alkalosis was not a factor, since the value for chlorides, the p_H and the carbon dioxide level were normal. Calcium and vitamin D administered orally over a long period brought the calcium toward normal levels.

43. Trangsrud, H. A.: Personal communication to the authors.

The macrocytic hyperchromic anemia present at the first admission to the hospital gradually changed to a normocytic hypochromic type after pancreatic juice alone was administered. During a severe remission macrocytes reappeared, but the smear became normal after liver therapy. The reticulocyte response was greatest after oral administration of liver extract at a time when the hemoglobin concentration and the erythrocyte count were lowest.

The severity of the disease is indicated by the continued low levels of plasma proteins and calcium, by the low maintenance level of the hematologic picture, by the low dextrose tolerance curve and by the constant hypotension.

SUMMARY

A commercial pancreatic preparation, Armour's pancreatin, was a valuable adjunct in treatment in a case of severe nontropical sprue and had the advantages of being readily available and well tolerated by the patient.

Pancreatic function appeared normal as tested by enzyme determinations on "fasting duodenal content," partition of fats and low excretion of nitrogen in the stool.

The clinical improvement of the patient when pancreatin or normal pancreatic juice was supplied suggests that there exists in certain cases of severe nontropical sprue a deficiency in some factor as yet undemonstrated.

Normal pancreatic substance or juice appears to provide this deficient factor valuable in intestinal digestion.

NORMAL BLOOD PRESSURE

ALAN E. TRELOAR, PH.D.
MINNEAPOLIS

A discussion of the range of normal blood pressures has been presented recently by Robinson and Brucer.[1] The authors have wisely emphasized the need for more accurate standards in judging the normality of any blood pressure level shown on clinical examination. In the paper of reference they essayed to provide such standards, based on "an exhaustive statistical study of 7,478 men and 3,405 women selected at random." Disregarding the possible clinical soundness of their deductions, it cannot be agreed that their method of analysis of the data is statistically sound. The study appears to have been characterized both by biased selection of the basic data and by application of frequency curve probablity values to distributions which certainly do not follow the function used. It is the purpose of this note merely to point out a few of the statistical errors that affect the validity of the conclusions. Unfortunately mere numbers of cases studied do not guarantee accuracy of the conclusions drawn.

It is well recognized in biostatistics that any attempt to fix limits of normal variation in a physiologic function is extremely hazardous. Nothing is more difficult to determine with satisfaction than the limits of range of a frequency distribution. When to this is added the confusing factor that the data under investigation represent a mixture of "normal" and "abnormal" values, there being no definition a priori of what constitutes physiologic normality, most fortunate conditions would have to prevail in order to make any thoroughly acceptable solution possible.

A brief consideration of the basic data is in order. Starting with a group of persons possessing life insurance and therefore originally selected by health criteria as good life insurance risks, the authors quickly passed to the statement that, because of time elapsed since the policies were issued, "our group comes close to being a typical portion of all age groups." Depending on the degree of closeness implied, one is led to the conclusion that the life insurance examination may have little value beyond perhaps rejecting those who are believed to be about

From the Division of Biostatistics, Department of Preventive Medicine and Public Health, University of Minnesota.

1. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409-444 (Sept.) 1939.

to die. One may well feel hesitant about accepting so extreme a conclusion. But, independently of this point, one must recognize that voluntary appearance for a periodic health examination is not likely to yield a random sample of the population of insured persons in any one category. It seems idle to conjecture whether there is a balance between those who fear to come because of known or suspected ailments which might influence the results of future application for more insurance and those who, secure in their contracts, come for a check-up when they fear that all is not well. It seems doubtful, then, whether the basic material was not a badly biased sample as far as the general population is concerned. However, Robinson and Brucer stated that it "comes close to being a typical portion of all age groups between 20 and 70 . . . and was taken under conditions of general health comparable to those of any random group in the total population."

It is in the statistical methods employed that the question of good reasoning comes most clearly into focus. After a thrust at the calculation of averages—"that most treacherous of statistical technics"—as normal values, they have sought shelter in modal values as better representations. One may well agree that averages are often misused, but does the "treachery" abide in the statistic any more than the blame for murder in the instrument employed to accomplish the end? The modal (or most frequently occurring) value is a useful element of descriptive information, to be sure, but a difficult one to determine objectively and with accuracy. Robinson and Brucer apparently used throughout their study an approximating expression which manages to shift the mode when a tail is cut away (or truncated) from the distribution. This is an obviously absurd result, for the value of most frequent occurrence is not affected by elimination of the values of comparatively rare occurrence.

In laying the ground for an arbitrary truncation of their distributions at 140 systolic and 90 diastolic to segregate the "abnormal" blood pressure groups, they gave the correlations of age with systolic and diastolic pressure for men as $+0.14 \pm 0.01$ and $+0.22 \pm 0.01$ respectively. The chances of such correlations arising solely through random sampling from an uncorrelated supply approach the infinitesimal, and yet they stated: "Neither of the correlations for men is significant." One would suspect here a confusion between statistical significance and practical importance. An accompanying graph, however, shows that the *average* systolic pressure for 7,478 men rose from 118 mm. at 35 years to about 148 mm. at 85 years. One would not be disposed to regard such an average change in blood pressure with age as unimportant from the practical point of view, and it certainly is statistically significant.

It has been assumed by the authors, however, that this rise is due to the presence of hypertensive persons in the total group, and so a

rejection level of 140 systolic and 90 diastolic has been arbitrarily chosen for elimination of the "abnormals." The inevitable consequence is that the correlation between age and blood pressure is markedly reduced for the remaining persons. But this reduction does not in itself constitute any justification whatever of the truncation. It is merely a method of forcing a desired result. It is not surprising, then, to read: "The exclusion of pressures over 140 systolic and 90 diastolic does not alter the conclusions of the analysis." The conclusion preceded the truncation!

In discussing the "delimited group," accepted *pro tempore* as normal with respect to blood pressure, Robinson and Brucer set probability ranges of variation, assuming the statisticians' normal frequency function values to be appropriate. This after arbitrary elimination of the upper 13 per cent of an obviously skew distribution! It has apparently been assumed that "normal" blood pressures follow the "law of error" distribution, which has unfortunately come to be known as the normal curve. It should be pointed out that this is an assumption for which no proof is advanced; many physiologic variables show a skew distribution rather than a normal one. But if the assumption is true in this case, the method used by the authors to estimate the parameters of the curve is altogether faulty in principle. An erroneous type of reasoning with respect to application of normal curve probabilities which occurs repeatedly throughout the paper is well manifested by the sentence: "With a standard deviation of 12.3 mm., it seems safe to conclude that the systolic blood pressures of this group of women, regardless of age, ranged from 100 to 125 mm." This is a range of one standard deviation on either side of the given mean. During a first course in statistics the student learns that for practical purposes the range of the normal curve may be taken as plus and minus 3 standard deviations from the mean. Plus and minus one standard deviation includes only 68 per cent of the cases, as the authors are apparently aware (p. 416). A tabulation directly below the statement just quoted shows that 11 per cent of this selected group of persons had pressures either below 90 or above 130 mm. By what conjuring does the range 100 to 125 mm. come to embrace all?

Probably enough questions have been raised already to warrant abstinence from further indulgence along this line. I wish to make it clear, however, that my objections to the paper of Robinson and Brucer do not center about the acceptability to physicians of the conclusions they have reached. These may conceivably be reasonably sound in spite of the absence of satisfactory supporting evidence. But to present such statistical manipulation as proof of the validity of the conclusions is to commit a serious offense against logical reasoning.

NECROBIOSIS LIPOIDICA DIABETICORUM

ALICE G. HILDEBRAND, M.D.*

HAMILTON MONTGOMERY, M.D.

AND

EDWARD H. RYNEARSON, M.D.

ROCHESTER, MINN.

Necrobiosis lipoidica diabeticorum is a localized cutaneous lipoidosis, most often encountered in association with diabetes mellitus. It should be distinguished from the true xanthomas because of the absence of xanthoma or foam cells. Clinically the condition is characterized by papular or plaquelike lesions, usually on the lower parts of the legs. Microscopically it is characterized by the presence of necrotic foci which contain droplets of various lipoids which lie in the deep layers of the cutis.

HISTORY AND INCIDENCE

The first instance of this relatively infrequent condition was described by Oppenheim [1] in 1929. The case was one of diabetes mellitus in which the typical cutaneous lesions appeared several years after the onset of diabetes. Oppenheim named this new condition "dermatitis atrophicans lipoides diabetica." In 1932, Urbach [2] described a similar case in which the condition was likewise associated with diabetes mellitus, and gave the disease its present name. Since these first 2 reports, approximately 65 others have appeared in the literature more or less completely, whereas 11 additional cases have been mentioned in connection with the reports of the other cases. The first case reported in the United States was described by Zeisler and Caro [3] in 1934. The first patient with this disease encountered at the Mayo

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* Fellow in Medicine, the Mayo Foundation.

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From the Section on Dermatology and Syphilology (Dr. Montgomery) and the Division of Medicine (Dr. Rynearson), the Mayo Clinic.

1. Oppenheim: Eigentümliche disseminierte Degeneration des Bindegewebes der Haut bei einem Diabetiker, Zentralbl. f. Haut- u. Geschlechtskr. **32**:179, 1929-1930.

2. Urbach, E.: Beiträge zu einer physiologischen und pathologischen Chemie der Haut: X. Eine neue diabetische Stoffwechseldermatose: Nekrobiosis lipoidica diabeticorum, Arch. f. Dermat. u. Syph. **166**:273-285 (Sept.) 1932.

3. Zeisler, E. P., and Caro, M. R.: Necrobiosis Lipoidica Diabeticorum (Urbach), Arch. Dermat. & Syph. **29**:167-169 (Jan.) 1934.

Clinic registered in 1936, and since that time 7 others have been studied here. The cases of these patients (to be described in this paper) together with those already reported in the literature represent a total of 86 which have been observed over the period of ten years since the first description of this condition. In addition to these 86 cases, which may be regarded as authentic, 8 others have been more or less completely described as examples of necrobiosis lipoidica diabeticorum but have been eliminated from this study either because of incompleteness of the report or because of doubtful findings in their description. In 2 of these cases the cutaneous condition occurred in association with diabetes mellitus (1 of Michelson's cases and 1 reported by Feldman [4]). In Michelson's [5] case cutaneous lesions were present at the site of injection of insulin and were not typical clinically of necrobiosis lipoidica. Feldman's case will be considered in detail further on in this report. In 4 of these doubtful cases the condition was not associated with diabetes mellitus. One, mentioned in connection with another case as observed by Chargin,[6] is not described further. In 1 case, reported by Bruce-Jones,[7] a microscopic picture much like that of a sclerosing type of sarcoid of tuberculosis was found. Giant cells were present, but lipoid was not demonstrated in sections. In 1 case, originally reported by Jamieson [8] as an example of necrobiosis lipoidica without diabetes mellitus, later there was found a blood sugar content of 225 mg. per hundred cubic centimeters; this case has been included in our cases in which diabetes mellitus was present. The fourth case, that reported by Greenwood and Rockwood [9] as an example of necrobiosis without diabetes mellitus, is not adequately described and hence is not included. Two other cases in which diabetes mellitus [10] was present and 1 in which it was not present, described in the literature, are likewise doubtful.[11]

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4. Feldman, S.: A Case for Diagnosis (Necrobiosis Lipoidica Diabeticorum? Xanthoma Diabeticorum with Necrosis?), Arch. Dermat. & Syph. **34**:326-328 (Aug.) 1936.

5. Michelson, H. E.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **34**:321-322 (Aug.) 1936.

6. Chargin, cited by Feldman.[4]

7. Bruce-Jones, D. B. S.: A Case Clinically Resembling Morphoea with a Tuberculous Background and Indeterminate Histology Suggestive of Necrobiosis Lipoidica, Brit. J. Dermat. **49**:238-240 (April) 1937.

8. Jamieson, R. C.: Necrobiosis Without Diabetes, Arch. Dermat. & Syph. **36**:912-913 (Oct.) 1937.

9. Greenwood, A. M., and Rockwood, E. M.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **35**:727-729 (April) 1937.

10. Nanta, A., and Bazex, B.: Nécrobiose dite lipoïdique des diabétiques, Bull. Soc. franç. de dermat. et syph. **45**:827-831 (May) 1938.

11. Hopkins, J. G., in discussion on Greenwood and Rockwood.[9]

ETIOLOGY

In more than 87.2 per cent of all cases of this dermatosis, including both those encountered elsewhere and those observed at the Mayo Clinic, diabetes mellitus has also been present. All of our patients and 70 of the 78 patients whose condition has been reported elsewhere had diabetes mellitus at the time of their initial visit. However, as will be pointed out later in our study, in some cases the cutaneous lesions preceded the onset of diabetes by as long as eight years. Among the remaining 10 per cent of patients who had such cutaneous lesions, evidence of diabetes has not yet appeared.

The incidence of this condition among the total number of diabetic patients seen since 1929 is impossible to estimate, because figures on the incidence of diabetes in the population as a whole are not available. However, some conception of its rarity may be gained from a consideration of our figures at the Mayo Clinic. Since the first case of necrobiosis was encountered, in 1936, a total of 8 have been studied. In that same period, 2,000 cases of diabetes have been encountered at the clinic.

Aside from the high incidence of diabetes, examination has failed to reveal the presence of any predominant associated disease which might have etiologic significance. Among the nondiabetic patients presenting these lesions, a fairly high incidence of vasomotor instability and hypertension (Boldt [12]) and 1 patient with a background of tuberculosis have been found. Among the patients who had diabetes, only 1 with active pulmonary tuberculosis and only 4 with positive tuberculin reactions have been described in the literature, although several have had hypertension. Tuberculosis was eliminated as a possible diagnosis in all of our cases. In only 1 case in the entire series was a positive Wassermann reaction obtained.

In connection with the etiology, there must also be considered the influence of the age of the patient at the time of onset of the lesions; sex; race; the duration, severity and degree of control of the diabetes; trauma at the site of the lesions, and, finally, the concentration of lipoids in the blood and tissues at the time of the first examination.

More than 80 per cent of all the patients with necrobiosis lipoidica were women. In 49 of the total of 78 cases reported in the literature the patients were women. Seven of the 8 patients seen at the clinic have been women. All of the patients in the entire series have been of the white race and of a wide variety of nationalities.

A study of the cases reported in the literature and those encountered at the clinic with regard to the age at which the cutaneous lesions first

12. Boldt, A.: Zur Kenntnis der Necrobiosis lipoidica ("diabeticorum"), Arch. f. Dermat. u. Syph. **179**:74-124 (May) 1939.

made their appearance reveals that this disease is primarily one of young persons. The commonest age at which the cutaneous lesions appear seems to lie between 10 and 40 years. In the cases reported in the literature, the age at the time of onset of the lesions (in the 47 cases in which this age was noted) ranged between 5 and 72 years, the average being 35 years. In all of the cases at the clinic, the age of onset ranged from 5 to 58 years, the average being 31.9.

The distribution of the cutaneous lesions according to age at the time of onset among the cases described in the literature is represented in table 1.

The age distribution of the patients seen at the clinic was as follows: 1 was 5 years of age at onset of the cutaneous lesions, 4 were between 20 and 30 years of age and 3 others were 43, 52 and 61 respectively, making a total of 5 who had the disease before the age of 40 years.

TABLE 1.—*Distribution of Cutaneous Lesions According to Age as Described in the Literature*

Age by Decades	Number of Cases	Percentage of Total Series
0- 9	4	8.5
10-19	9	19.2
20-29	7	14.9
30-39	10	21.3
40-49	8	17.0
50-59	6	12.7
60-69	3	6.4
Mean age	33	Average age 35.0
Less than 40	30	63.8
More than 40	17	36.2

A closer study of these figures reveals that in about 64 per cent of all cases encountered elsewhere and in about 60 per cent of all cases encountered at the clinic, cutaneous lesions developed prior to the age of 40 years; that is, 62.2 per cent of all patients whose ages at the time of onset of the cutaneous lesions were recorded had these lesions before the age of 40 years. Of this group itself, 57.1 per cent had such lesions during the second and third decades of life.

A study of the ages at the time of onset of diabetes mellitus and the ages at the time of onset of the cutaneous lesions revealed that although in the majority of the cases encountered elsewhere and at the Mayo Clinic the cutaneous lesions had developed after onset of the diabetes, in a certain small percentage of cases in both series the reverse was true. This relation between the onset of the diabetes and the onset of the cutaneous lesions may be seen from an examination of table 2.

Although in 55.6 per cent of the cases reported elsewhere diabetes was diagnosed one to ten years or more prior to the appearance of the cutaneous lesions (seventeen years in 1 of Boldt's cases), in 7 cases

in the literature, or in 17.8 per cent of the whole series (this includes only those cases in the literature in which the ages at the time of onset of diabetes and of the cutaneous lesions are given), a history of development of the cutaneous lesions prior to the onset of diabetes was obtained. Klaber [13] described a case in which a history of cutaneous lesions dated back five years prior to the time of examination, without symptoms of diabetes but with a value for blood sugar of 300 mg. per hundred cubic centimeters at the time of examination.

Michelson [14] later reported a case in which cutaneous lesions appeared two years prior to the onset of diabetes. Bernstein [15] reported a case in which there were symptoms of diabetes of eight years' duration but in which the cutaneous lesions dated back nine years. Gross and Machacek [16] described a case in which the diabetes was discovered three years after the first appearance of the cutaneous lesions. Riehl [17] reported a case in which the cutaneous lesions preceded the diabetes by three years. Boldt described 2 cases in which the cutaneous lesions appeared one and five years, respectively, prior to the onset of

TABLE 2.—*Relation Between Onset of Diabetes Mellitus and Onset of Cutaneous Lesions as Reported in the Literature*

Cutaneous Lesions Prior to Diabetes Mellitus			Simultaneous Onset		Cutaneous Lesions After Diabetes Mellitus		
Years Prior	Number	Per Cent of Total	Number of Cases	Per Cent of Whole Series	Years After	Number	Per Cent of Total
1	2	25.0	..	....	1	7	28.0
2	1	12.5	12	....	2	7	28.0
3	2	25.0	..	27.3	3	3	12.0
4	0	0.0	..	....	4	1	4.0
5	2	14.5	..	....	5	3	12.0
8	1	....	..	....	6	0	0.0
..	..	....	..	....	7	1	4.0
..	..	....	..	....	8	1	4.0
..	..	....	..	....	9	0	0.0
..	..	....	..	....	10 and greater	2	8.0
Totals.....	8		12			25	
Whole series, 45 cases							
Per cent of whole series		17.8		26.6			55.6
Average difference		42 months				40.3 months	

13. Klaber, R.: Necrobiosis Lipoidica Diabeticorum: Report of a Case, Brit. J. Dermat. **46**:226-228 (May) 1934.

14. Michelson, H. E.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **33**:900 (May) 1936.

15. Bernstein, J. C.: Necrobiosis Lipoidica Diabeticorum (Urbach): Comparison with Granuloma Annulare, Arch. Dermat. & Syph. **36**:282-286 (Aug.) 1937.

16. Gross, P., and Machacek, G. F.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **32**:491-494 (Sept.) 1935.

17. Riehl, G., Jr.: Necrobiosis lipoidica diabeticorum, Zentralbl. f. Haut- u. Geschlechtskr. **57**:11, 1937-1938.

diabetes. Among those patients who had diabetes before the cutaneous lesions developed, the discovery of the former antedated the onset of the latter by an average of forty-two months. Among those of whom the reverse was true, the cutaneous lesions preceded the diabetes by an average of forty and three-tenths months. In 12 cases, representing 27.3 per cent of the whole series, the cutaneous lesions and the symptoms of diabetes were recognized at approximately the same time.

Considering the series as a whole, the average duration of the cutaneous lesions at the time when the patient was seen was six and three-tenths years. The duration of the diabetes at the time of the first examination ranged from several months to ten years, with an average duration of eight and six-tenths years. Therefore, on the average the onset of diabetes mellitus preceded that of the cutaneous lesions by two and three-tenths years among all the cases.

Of the 8 patients seen at the clinic, 5 had cutaneous lesions four months to three years after the onset of diabetes, an average of nineteen months. In 2 cases the cutaneous lesions appeared one and two years, respectively, prior to the appearance of glycosuria. In 1 of our cases diabetes and the cutaneous lesions appeared almost simultaneously. Considering the entire series, the average duration of the cutaneous lesions at the time when the patient was first seen was four years. The duration of diabetes at the time of the first examination ranged from several months to eleven years with an average duration of three and two-tenths years. Therefore, on the average, the onset of diabetes preceded that of the cutaneous lesions by almost ten months.

The severity of diabetes in the cases reported in the literature varied widely. However, in more than 70 per cent it could be classified as moderately severe or severe. Despite this fact, Hitch,[18] in reviewing 20 of the cases reported prior to September 1937, made the statement that " . . . apparently the condition [the necrobiosis] is not dependent on the severity of the diabetes or the extent of the hyperglycemia." In all of our cases the condition was classified as grade 3 (moderately severe), or grade 4 (severe). For all the cases in the literature the average value for "fasting blood sugar" on the first examination was 246.2 mg. per hundred cubic centimeters, whereas for the cases observed at the clinic the average value on admission was 317.7 mg.

Perhaps of more significance than the severity of the diabetes at the time when the patients were first seen is the factor of previous control of their disease. In the majority of cases of necrobiosis lipoidica diabeticorum, both those reported elsewhere and those encountered at the clinic, the course has been very poorly controlled throughout the disease. In many cases histories of repeated episodes of acidosis

18. Hitch, J. M.: Necrobiosis Lipoidica Diabeticorum (Urbach and Oppenheim), Arch. Dermat. & Syph. **36**:536-543 (Sept.) 1937.

were obtained. All of our patients, with 1 exception, and most of those observed elsewhere had been treated with insulin during the greater part of their course. Some authorities have considered that the use of insulin may have had a role in the development of the cutaneous lesions. Michelson reported a case in which lesions developed at sites at which insulin had been injected. However, as has been mentioned, this was a very doubtful case of necrobiosis lipoidica. O'Leary, in considering 1 of the cases reported by Michelson,[19] stated: "Local reaction to injections of insulin at the same site may result in a gangrenous slough or simply in fatty necrosis without cutaneous gangrene, leaving depressed scars. This new entity (necrobiosis lipoidica diabeticorum) may be the result of the use of insulin, in that the insulin, although not injected in the vicinity of the cutaneous lesions,

TABLE 3.—*Relation Between Onset of Diabetes Mellitus and Cutaneous Lesions in Clinic Series*

Lesions Prior to Diabetes			Simultaneous Onset		Lesions After Diabetes		
Years Prior	Number	Per Cent of Total	Number of Cases	Per Cent of Whole Series	Years After	Number	Per Cent of Total
1	1	50.0	1	14.3	1	3	60.0
2	1	50.0	..	....	2	1	20.0
3	..	....	..	....	3	1	20.0
Totals.....	2		1			5	
Whole series, 8 cases							
Per cent of whole series		25.0		12.5			62.5
Average difference		1.5 years (18 months)				1.5 years (19 months)	

may produce vascular injury, or precipitate, in vessels already sclerotic, sufficient damage to result in this new cutaneous picture." In none of our cases did the lesions develop at the sites of injection of insulin. Furthermore, instances of allergic phenomena, such as urticaria, which might be traced to the injection of insulin have not been observed in any of the cases studied at the clinic and have not been reported in connection with any of the cases encountered elsewhere. Finally, as has been mentioned, in 8 instances among the cases reported elsewhere and in 2 of the cases encountered at the clinic the cutaneous lesions developed prior to the onset of diabetes mellitus. Also, in 8 cases in which there were typical lesions, evidence of diabetes was not found. Reaction to injection of insulin could have played no part in the development of the cutaneous lesions in these cases.

Trauma seems to play a definite role in the causation of this condition. From 12 to 16 per cent of the patients seen elsewhere and at least 1 of those studied at the clinic stated that some type of injury had

19. Michelson, H. E.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **30**:897-898 (Dec.) 1934.

occurred at the site of the cutaneous lesions prior to their development. Bruises, cuts, scratches and mosquito bites were noted among the preceding injuries. In 2 instances, lesions in the papular stage advanced rapidly to a state of ulceration after trauma.

Diet prior to onset of the cutaneous lesions is apparently not a factor of great significance. Only 3 of the patients in the entire series, 1 of them among those seen at the clinic, had been on a diet high in fat at some time during the course of diabetes. Most of the patients had been on a diet relatively high in carbohydrates prior to the onset of the cutaneous lesions. None of the patients seen at the clinic was overweight at the time of examination.

In 8 cases in which diabetes mellitus was not present, 7 reported by Boldt and 1 by Goldsmith,[20] there were cutaneous lesions which were identical grossly and microscopically with those seen in the cases in which diabetes was present, but there were no symptoms of diabetes, and on examination normal dextrose tolerance curves were found. Goldsmith reported a case in which the lesions, both clinically and histologically, were necrobiosis lipoidica and in which the Mantoux reaction was positive with a dilution of 1:10,000 (old tuberculin). There were no signs of active tuberculosis. Goldsmith also mentioned another case in which the lesions grossly resembled necrobiosis lipoidica but microscopically represented the picture of cutaneous tuberculosis. In this case a diagnosis of scleroderma-like erythema induratum was made. Goldsmith regarded this condition and necrobiosis lipoidica diabeticorum as different phases of the same disease.

MORBID ANATOMY

The lesions described in the literature, as well as those observed in our cases, have followed, in general, a comparatively definite pattern both macroscopically and microscopically. Among the cases in the literature, complete descriptions of the lesions were given in 54 instances, with histologic descriptions in 35. In all of our cases we have descriptions of the gross appearance of the lesions, but in only 3 were there microscopic studies as well.

Grossly, these lesions may represent one phase of the disease or several at the same time. Usually the lesions are asymptomatic, although in some cases itching and burning have been complained of. The most common site of occurrence of these lesions is on one leg or both legs below the knees. In approximately 85 per cent of all cases reported elsewhere and in 82 per cent of our cases the lesions have occurred at this site. Bilateral lesions were present in approximately 54 per cent of the cases observed elsewhere and in 75 per cent of our

20. Goldsmith, W. N.: Necrobiosis Lipoidica, Proc. Roy. Soc. Med. **28**:363-364, 1935.

cases. In 6 of the cases reported elsewhere one or both arms were involved, whereas in our series 1 patient had involvement of the wrists. In this case the legs also were affected. Other sites of occurrence which have been reported include the thighs, abdomen, breasts and (in Oppenheim's case) almost the entire cutaneous surface. From one to fifteen lesions have been reported in an individual case, but the average number of lesions found in each case among those reported elsewhere was five at the time of examination.

According to Hitch, the typical lesions may go through four phases: (1) a small, reddish, infiltrated papule, (2) an increasingly larger lesion which takes on a violescent hue, (3) a slightly raised, firm yellow plaque, which may soften and sometimes may ulcerate and (4) a flattened, yellowish region with central atrophy and depression and a peripheral irregular scaling red or violescent region of infiltration. The color is due to the amount of lipoids deposited in the connective tissues, secondary deposition of hemosiderin and a variable amount of stasis in the underlying blood vessels.

In the majority of the cases encountered elsewhere the course of the lesions followed this pattern closely. The lesions usually started as firm papules and progressed to plaque formation with or without subsequent ulceration. The plaques ranged from 1 by 2 cm. to 3 by 5 cm. In the course of months, many of these lesions became transformed into atrophic scars covered with fine scales. In approximately a fourth of these cases the lesions were papules at the time of examination; in more than 50 per cent there were plaques, which were round, oval or irregular. Among our cases, in 2 there were papular or nodular lesions; in 5, plaques, and in 3 depressed scars accompanying the other lesions. The literature records depressed and atrophic scars in more than a third of the cases. Ulceration of the lesions occurred in only a quarter of the total cases as compared with an incidence of 50 per cent among our cases. In 2 cases reported in the literature, cultures of the material from these ulcers on ordinary mediums yielded negative results. In 1 of our cases similar cultures yielded gram-positive cocci.

Central xanthochromia has been observed frequently in the lesions of necrobiosis lipoidica. In two thirds of the cases reported in the literature and in half of the cases encountered at the clinic this feature was present. Likewise, a violescent or reddish brown border is often found in these lesions, having been reported in almost 60 per cent of the cases in the literature and in 50 per cent of our cases; usually these borders are well defined. The surface of the lesions showed dry, adherent scales in about 30 per cent of the cases in both series, and, in addition, telangiectasis of the surface occurred in 50 per cent of our patients as compared with an incidence of almost 45 per cent among

the patients seen elsewhere. Black central crusting was noted in 20 to 25 per cent of the cases in both series.

Histologic studies of these lesions revealed that the greatest changes occurred in the deep layers of the cutis. In almost half of the 21 cases in which microscopic studies were made there were minor changes in the epidermis, however, including hyperkeratosis, intercellular edema and flattening of the rete ridges. The granular layer, except in 1 instance, was intact throughout. In only 2 cases were there any changes in the papillary layer of this cutis; in these the changes consisted of a moderate amount of vascular dilatation and perivascular infiltration. Among the remaining cases, the entire pathologic change occurred in the subpapillary layers of the cutis.

The histopathologic picture is characterized by necrobiotic rather than true necrotic changes in the collagen fibers, consisting in homogenization and degeneration of the fibers together with loss of elastic tissue and a peripheral perivascular inflammatory reaction involving chiefly connective tissue cells, various types of histiocytes, lymphocytes and occasionally leukocytes and plasma cells. Varying degrees of obliterative change were encountered in the smaller blood vessels, which are surrounded by the infiltrate and thus account for the necrobiotic changes in the collagen fibers in the center of the plaques. Varying amounts of lipoids were observed, chiefly in the center of the lesions in the region of degeneration of the collagen fibers. These lipoids stained reddish brown with sudan III and did not show double refraction with the polariscope. Most authors feel that these lipoids are composed of phospholipids and free cholesterol. Most of the fat lies extracellularly, although occasionally small, intracellular deposits are seen in the chromatophores, without, however, their being typical xanthoma or foam cells, such as are characteristic of the usual types of xanthoma. Xanthoma cells were reported present in 1 case of necrobiosis by Feldman, but the diagnosis in this case was questionable, as the distribution and characteristics of the lesions were those of xanthoma diabeticorum. The patient had marked elevation of the concentration of lipoids in the blood, and the lesions involuted promptly under a proper dietary regimen and injections of insulin. In 2 cases [21] reported in the literature as examples of necrobiosis lipoidica, extracellular double refracting crystals were found. In none of our 3 cases was this phenomenon observed. Giant cells were reported in 4 cases in the literature but were more of the foreign body type than of the Touton type of giant cell which is characteristic of ordinary xanthoma. Depositis of hemosiderin in the necrobiotic areas were a common finding in cases studied elsewhere, and they were a uniform finding in the 3 cases studied at the clinic.

21. Klaber, R.: Necrobiosis Lipoidica Diabeticorum, Proc. Roy. Soc. Med. **30**:976, 1937.

DIAGNOSIS

It should be possible to make a diagnosis of necrobiosis lipoidica diabeticorum on the clinical appearance of the lesions alone. The finding on the lower extremities of flattened plaques with yellowish centers surrounded by violescent or red-brown borders, with or without central ulceration, especially in a known case of diabetes mellitus, is characteristic. These lesions differ considerably from those of the other types of xanthomatosis, which are usually firm, yellowish papules occurring on the extensor surfaces of all four extremities. The finding of intracellular deposition of lipoids in foam cells in the latter lesions makes recognition final. Xanthoma diabeticorum is a typical xanthoma both macroscopically and microscopically, and the lesions, unlike those of necrobiosis lipoidica, can be made to improve rapidly by proper management of the diabetes.

Other necrotic lesions which occur in association with diabetes mellitus may be confused with necrobiosis lipoidica. Localized necrosis of the extremities may follow trauma to these parts in cases of diabetes mellitus. These lesions are usually solitary rather than bilaterally symmetric, are moist rather than dry and may be so deep that they involve the subcutaneous tissues. A spontaneous nontraumatic variety of localized necrosis may also occur in cases of diabetes mellitus. In this type the eruption may vary in bilateral symmetry and may appear as gangrenous patches of variable depth which are preceded by bullae or as small, dry gray or black gangrenous patches which involve hardly more than the corium and which, after several days, separate to leave a granulating, slowly healing surface. Microscopic examination of any of the lesions reveals destruction of all types of tissue in the involved regions, not the pseudonecrotic degeneration of the collagen fibers with complete loss only of the elastic fibers seen in cases of necrobiosis lipoidica. Furthermore, any of these lesions will heal with proper treatment of the diabetes.

Lipoid proteinosis is, like necrobiosis lipoidica, a form of extracellular xanthomatosis, and like necrobiosis lipoidica it tends to occur in association with diabetes mellitus. However, the clinical appearance of the lesions differs greatly from that seen in cases of necrobiosis. Also, the lesions often involve the mucous membranes in cases of lipoid proteinosis, never in cases of necrobiosis. Furthermore, patients who have the former disease have an increase of lecithin in the blood and tissues. Microscopically the two conditions differ in that in lipoid proteinosis there is a homogeneous lipoid deposit in the connective tissue and around the blood vessels extracellularly, and there is not the marked necrosis of the connective tissue seen in cases of necrobiosis lipoidica.

The papular form of necrobiosis lipoidica may be confused with the reddish papules of so-called extracellular cholesterosis or of amy-

loidosis. However, one of us (Montgomery) believes that the former represents simply a fibrous end stage of xanthoma tuberosum, and foam cells can still be demonstrated in the lesions. The latter condition shows homogeneous masses in the papillary and subpapillary layers of the corium which give a positive stain for amyloid.

Granuloma annulare may be microscopically and even clinically similar to necrobiosis lipoidica. Bernstein studied sections of the lesions in 4 cases of granuloma annulare, 3 in which diabetes mellitus was ruled out and 1 in which diabetes mellitus had been present for eight years. The sections were stained with sudan III, and none of them showed sudanophilic droplets between the collagen fibers. This is contrary to what is usually true of necrobiosis lipoidica.

STUDIES ON PATHOGENESIS

Since this condition represents essentially a lipoid disturbance of the skin, some alteration in the lipoid content of the blood and tissues has been sought as a possible explanation for the appearance of these lesions. In 39 of the cases encountered elsewhere the cholesterol content of the blood has been determined, whereas in only 6 of these cases have complete studies of the blood lipoids been made. In all of the cases seen at the clinic complete determinations of blood lipoids have been made. Only 4 cases in the entire series, 2 at the clinic, 1 reported by Usher and Rabinowitch [22] and 1 reported by Zeisler and Caro,[23] have been studied from the standpoint of the lipoid constituents of the tissue itself.

Correlation of the values for blood lipoids found elsewhere and those found at the clinic is difficult because of the different methods of analysis used. In many of the cases reported elsewhere older methods of analysis have been used; hence only approximate comparisons can be made with our figures.

In all of our cases the studies on the blood lipoids were made in the morning, before the patients had had breakfast, and the procedures were carried out on plasma. In some of our cases older methods of analysis may have been used, but in most the cholesterol was determined by the methods of Bloor;[24] lecithin, in some instances by the method of Whitehorn [25] and in others, especially the more recent ones, by that

22. Usher, B., and Rabinowitch, I. M.: Necrobiosis Lipoidica Diabeticorum: Report of a Case with Clinical, Pathologic and Biochemical Observations, Arch. Dermat. & Syph. **35**:180-187 (Jan.) 1937.

23. Zeisler, E. P., and Caro, M. R.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **30**:299 (Aug.) 1934.

24. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227-231, 1916.

25. Whitehorn, J. C.: A Method for the Determination of Lipoid Phosphorus in Blood and Plasma, J. Biol. Chem. **62**:133-138 (Nov.) 1924.

of Youngburg and Youngburg,[26] and the total lipoids by the technic outlined by Bloor.[27] The concentration of these same substances in tissue was estimated by the same procedures on the alcohol-ether extract of the tissues. In all 4 instances in which a determination of the tissue lipoids has been made the figures for the various lipoids are given as percentages of the wet weight of the specimen. In all instances, also, the subcutaneous fat and adjacent normal tissue were carefully trimmed from the necrobiotic nodule, and immediate analysis was made. In the case reported by Usher and Rabinowitch the skin near the necrobiotic nodule was also studied chemically for comparison; in these instances also the subcutaneous fat was cut off before the analysis was made.

The normal figures for blood lipoids in use at the Mayo Clinic at the time the blood and tissue analyses on our patients were made, as

TABLE 4.—*Values for Lipoid Constituents*

	Mg. per 100 Cc. Plasma		
	Older Figures (Montgomery and Osterberg)		New Figures (Barker) Average Mean
Lipoid Constituents	Range of Values	Average	Normal
Total cholesterol	160-200	180	218
Cholesterol esters	110-145	125	154
Lecithin	200-250	225	223
Total fatty acids	335-350	345	350
Total lipoids	500-550	525	565

well as the figures recently determined at the clinic as the average mean normal values for the various lipoids, are given in table 4.

The new figures given in this table represent the average mean normal values as found in recent studies conducted at the clinic on 200 presumably normal subjects by the committee on blood lipoids (Barker, Montgomery, Osterberg, Willius and Wilder) and are to be reported in a forthcoming paper by Barker.[28] These studies have revealed an even wider variation in normal values for all the blood lipoids than did the older figures previously considered as normal values and, on the whole, higher values for the various lipoids in the third and fourth decades of life. Further studies on blood lipoids are contemplated in regard to correlating the values not only with age groups but with sex and with the presence or absence of such complicating factors as obesity

26. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. **16**:158-166 (Nov.) 1930.

27. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53-73 (April) 1928.

28. Barker, N. W.: The Plasma Lipoids in Arteriosclerosis Obliterans, Ann. Int. Med. **13**:685-692 (Oct.) 1939.

and pregnancy. It is worthy of note that the upper limits of normal given in the older set of figures closely approximate the new average mean normal figures.

The normal figures for the lipoids of the skin likewise vary considerably. For a complete review of the work done on tissue lipoids, reference may be made to a recent paper by Montgomery and Osterberg.[29] These authors came to the conclusion that "the amount of total lipoids of the normal skin averages less than 3 per cent of the wet weight, that from 5 to 15 per cent of these total lipoids is in the form of cholesterol (most of it being in the free form), and that the lecithin varies from only a trace up to 30 per cent of the total lipoids." Table 5 represents a summary of values for the blood lipoids as noted both at the clinic and elsewhere.

In the total series of cases studied elsewhere the only blood lipoid which has been studied in a significant number of cases is cholesterol.

TABLE 5.—*Summary of Values for Blood Lipoids*

Lipoids	Average Mean Normal		Cases Seen Elsewhere			Cases at the Clinic	
	Older	New	Number	Range of Values	Average Value	Range of Values	Average Value
Cholesterol.....	180	218	39	129-720	271	131-248	210.5
Cholesterol esters.	125	154	16	74-370	163	87-177	137
Lecithin.....	225	223	6	178-625	372	192-250	219
Fatty acids.....	345	350	11	421-657	559	269-500	346
Total lipoids.....	525	565	6	700-1,500	995	401-728	551

This was determined in 39 cases, and, as may be seen from table 5, the average value for this lipoid constituent of the blood is somewhat, but not markedly, greater than our average mean normal values. However, the significance of this finding is rather doubtful, as in only 2 cases of the entire series have cholesterol ester crystals been found in the lesions themselves, although, as will be shown later, in 2 of the 4 cases in which tissue lipoid studies were made the values for tissue cholesterol were somewhat greater than normal. In the clinic series, from which more accurate comparisons may be made, the average value for cholesterol was almost identical with the new average mean normal value as reported by Barker. It is of interest to note that in 1 of the cases in which cholesterol ester crystals were observed in the lesions (Klaber), two estimates of the value for blood cholesterol were within normal limits, being 166 mg. and 195 mg. per hundred cubic centimeters respectively. None of our patients have shown cholesterol ester crystals in the lesions. Urbach[30] reported a patient

29. Montgomery, H., and Osterberg, A. E.: Xanthomatosis: Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch. Dermat. & Syph. **37**:373-402 (March) 1938.

30. Urbach: Necrobiosis Lipoidica Diabeticorum, Dermat. Wchnschr. **99**:1596 (Dec. 8) 1934.

who on funduscopic examination was found to have glittering particles in both retinas; he thought that these particles might have been cholesterol.

In the small number of cases reported in the literature in which complete studies of the blood lipoids have been made, all of the values for lipoid constituents, besides cholesterol, have been elevated to a variable extent. The values for cholesterol esters have ranged from 74 to 370 mg. per hundred cubic centimeters, with an average of 163 mg.; those for lecithin, from 178 to 625 mg. per hundred cubic centimeters, with an average of 372 mg.; those for fatty acids, from 421 to 657 mg. per hundred cubic centimeters, with an average of 559 mg., and those for total lipoids from 700 to 1,500 mg. per hundred cubic centimeters, with an average of 995 mg. As has been pointed out, these figures are difficult to evaluate: first, because of the variation in the types of analysis used; second, because the number of cases in which complete studies of the blood lipoids were made is small, and third, because the range in the values for each lipoid constituent of the blood varies greatly with different methods of analysis and, as Barker has shown, also with the different age groups. Hence most of the figures given in the literature lie very close to the ranges of normal values. The values for blood lipoids in the case reported by Feldman have not been included in these calculations because, as has been mentioned, this was not clearly a case of necrobiosis lipoidica.

Marble [31] has said that in 6 of 9 cases which he has encountered, none of which has been completely reported, at one time or another there were total cholesterol values above 230 mg. per hundred cubic centimeters, but none higher than 312 mg. In all cases the ratio of cholesterol esters to total cholesterol was normal. In 2 instances the values for total lipoids were more than 800 mg. per hundred cubic centimeters, and in these cases the phosphatide content of the blood also was elevated. In addition, Marble stated that there is usually a moderate increase in all of the lipoid elements of the blood in cases of necrobiosis lipoidica but that the same degree of increase is also seen in cases of diabetes mellitus without necrobiosis.

The study on the blood lipoids in this condition at the clinic was done in all 8 cases. Also, complete quantitative analysis of the lipoid constituents of tissue was made in 2 cases. As indicated in table 5, comparison of the average normal values for each of the blood lipoids as found in these 8 cases with the recently obtained average mean normal values of Barker reveals them to be almost identical. Furthermore, in every instance the range of values for the individual lipoids in these 8 cases corresponded very closely with the range of values for these lipoids for the same age groups among the normal subjects studied

31. Marble, A., in discussion on Greenwood and Rockwood.[9]

by Barker and his co-workers. On the whole, therefore, it may be said that our studies of blood lipoids in cases of necrobiosis lipoidica have yielded negative results.

Although quantitative determinations of the lipoid constituents of the tissues have been made in only 4 cases, several investigators have made qualitative studies on sections from the lesions by means of selective staining. Michelson and Laymon,[32] Balbi [33] and Zeisler and Caro [23] have reported that the fat droplets in these lesions consist of phospholipids and neutral fats. Usher and Rabinowitch [22] have reported that in 1 case the free cholesterol found in the tissues was five times that found in normal skin.

The values for the tissue lipoids in the 4 cases in which they have been determined quantitatively are indicated in table 6. As in the case of the blood lipoid determinations, the significance of the figures obtained

TABLE 6.—*Values for Tissue Lipoids*

Lipoid Constituent	Usher and Rabinowitch		Clinic Case 1		Clinic Case 2		Zeisler and Caro	
	% Wet Weight	% Total Lipoids	% Wet Weight	% Total Lipoids	% Wet Weight	% Total Lipoids	% Wet Weight	% Total Lipoids
Cholesterol, total	2.20	26.5	0.43	20.9	0.30	2.21	0.554	8.9
Cholesterol, esters	0.19	2.3	0.40	19.4	0.20	1.48	.....	...
Cholesterol, free	2.02	24.3	0.03	1.5	....	....	.....	...
Phospholipids	0.24	2.9	0.13	6.3	0.044	0.324	0.397	6.4
Phospholipids as lecithin	6.00	72.3	3.20	155.3	1.10	8.09	9.930	159.0
Fatty acids	....	....	1.63	79.1	13.40	98.53	.....	...
Total lipoids	8.30	....	2.06	....	13.60	....	6.21	...

is questionable. As has been mentioned, the values found by various investigators for the lipoid constituents of normal skin vary greatly. If these figures are compared with those given by Montgomery and Osterberg, it would appear that in 3 cases (that of Usher and Rabinowitch, that of Zeisler and Caro and 1 of ours) the values for total lipoids were high, for Montgomery and Osterberg concluded that the total tissue lipoids should represent, on the average, less than 3 per cent of the total wet weight of the specimen examined. Figures given by Usher and Rabinowitch on a section of normal skin from the same patient whose necrobiotic lesions they studied chemically are in close agreement with those given as normal by Montgomery and Osterberg. Usher and Rabinowitch found in this normal skin 3.30 per cent of total lipoids, of which the total cholesterol equaled 0.50 per cent (15.1 per cent of the

32. Michelson, H. E., and Laymon, C. W.: Necrobiosis Lipoidica Diabeticorum (Urbach); Dermatitis Atrophicans Lipoides Diabetica (Oppenheim), J. A. M. A. **103**:163-169 (July 21) 1934.

33. Balbi, E.: Ricerche intorno alla patogenesi della necrobiosis lipoidica diabeticorum Urbach-Oppenheim, Gior. ital. di dermat. e sif. **74**:14-43 (Feb.) 1933; abstracted, Arch. Dermat. & Syph. **28**:572-573 (Oct.) 1933.

total lipoids), the cholesterol esters 0.07 per cent (2.1 per cent of the total lipoids), the free cholesterol 0.45 per cent (13.9 per cent of the total lipoids) and the lecithin 1.50 per cent (45 per cent of the total lipoids). In 3 of these cases, also, the lecithin was higher than normal, especially in our first case and in the case reported by Zeisler and Caro, in which the lecithin represented 155 per cent and 159 per cent, respectively, of the total lipoids. In 2 of the 4 cases the total cholesterol was elevated when compared with the 5 to 15 per cent of the total lipoids given as normal by Montgomery and Osterberg. In our first case it represented 20 per cent of the total lipoids; in the case reported by Usher and Rabinowitch, 26.5 per cent of the total lipoids. In our case most of the cholesterol was in the combined form, which is the reverse of what was found in the case reported by Usher and Rabinowitch.

The values for fatty acids were determined only in our cases. In our second case these were markedly elevated, representing 98.5 per cent of the total lipoids, of which only 8.09 per cent was in the form of lecithin. In this case we suspected but were not able to prove that not all of the subcutaneous fat was trimmed off prior to analysis, so that an excessive amount of neutral fats may have been included.

The pathogenesis of this condition, therefore, remains obscure. Because of the high incidence of vascular changes seen in the lesions of necrobiosis lipoidica, many authors have assumed that this disease is essentially due to damage to the small blood vessels of the corium, possibly by circulating toxins, with subsequent thrombosis, necrosis and secondary imbibition of fat particles. Reasoning along this line, one might suppose that if vascular injury plays a prominent role in the development of the cutaneous lesions, evidence of vascular damage at other sites should be found in the majority of cases. As has been mentioned, Boldt found a high percentage of instances of vasomotor instability and many instances of hypertension. However, in only 3 or 4 of the cases encountered elsewhere were the vessels of the extremities reported as sclerotic, and in only a few were changes in the retinal vessels reported. In our series, only 1 patient had any degree of sclerosis of the peripheral vessels, although in 3 changes in the retinal vessels were found. In the 1 case in which peripheral sclerosis occurred, this was of such a degree that amputation of one leg was necessary. Microscopic studies of the vessels in this case showed intimal proliferation and deposition of fatty particles in the regions of proliferation. However, these changes in the patient, a 60 year old woman, may have been entirely related to her age, because elderly patients who have arteriosclerosis present essentially these same pictures. Indeed, the vessels of two lower extremities removed from 2 elderly patients who had diabetes mellitus and who did not have necrobiosis were studied here, and there was found practically the same histologic picture as that observed in

the case in which necrobiosis was present. It should also be pointed out in this connection that many diabetic patients have changes in both the retinal and the peripheral vessels of as great a degree as was shown by any of the patients who had necrobiosis, although they had not yet experienced the development of cutaneous lesions. However, failure to find generalized arteriosclerosis in any considerable number of cases of necrobiosis cannot be considered as absolute evidence against the hypothesis of primary vascular damage as a background for these lesions, because localized arteriolar damage (in the skin, for example) has been known to occur in the absence of generalized vascular changes.

The other hypothesis which has been considered is that the cutaneous lesions are secondary to changes in the general metabolism of fat. However, as has already been pointed out, the blood lipoids have not been found to be constantly altered, and the significance of the changes found in the tissue lipoids is questionable. Furthermore, there is no reason to assume that there has been any alteration in the metabolism of fat of the 8 patients who did not have diabetes mellitus, although in the only cases in which any studies of the blood lipoids were made the results are at variance with each other. In the cases reported by Goldsmith only a determination of cholesterol was made, and the value, 150 mg. per hundred cubic centimeters, was within normal limits. In 3 cases in which diabetes was not present, reported by Boldt, the value for blood cholesterol was more than 200 mg., 239 mg. and 233 mg. per hundred cubic centimeters respectively. In 3 of his cases, also, the values for fatty acids were somewhat elevated (485 mg., 400 mg. and 614 mg. per hundred cubic centimeters). It should be pointed out, too, that the presence of diabetes mellitus itself in these cases of necrobiosis occurring in association with the former disease may have been responsible for any alteration found in the blood lipoids.

TREATMENT

Treatment, either local or general, for those patients who have diabetes mellitus has been of little avail in the majority of cases in which necrobiotic lesions are present. These lesions typically run an indolent, chronic course, either slowly enlarging over a period of months or years or slowly receding to form depressed scars. Control of the glycosuria with proper diet and insulin seems to have little effect on them, although some authors (Feldman; Klaber[34]; Kren[35]) have reported good results with diets low in fat. Three of the patients at the

34. Klaber, R.: Necrobiosis Lipoidica Diabeticorum (Urbach-Oppenheim), Proc. Roy. Soc. Med. **27**:713-714, 1934.

35. Kren: Necrobiosis lipoidica diabeticorum, Zentralbl. f. Haut- u. Geschlechtskr. **49**:580, 1934-1935; **55**:186 and 614-615, 1936-1937; **58**:2-3, 1938.

clinic were placed on this type of diet, but no improvement occurred in the period of observation (several months to a year).

Local treatments have been of a wide variety. Several authors (Urbach; Zeisler and Caro) have tried injection of insulin at the site of the lesions. In no instance has this treatment resulted in healing of the lesions. Ultraviolet light therapy, irradiation and various local medications have been equally unsuccessful in accelerating healing of these lesions.

REPORT OF CASES

CASE 1.—A white American woman aged 31 was first seen at the clinic in June 1936. She related a long family history of diabetes mellitus in both her mother's and her father's families. The patient had one sister, who was living and who had diabetes. The patient had classic symptoms of diabetes for the first time in 1926; at that time she was given a weighed diet. Twelve units of unmodified insulin was administered morning and evening. Shortly thereafter the diet was changed to a qualitative one, which she had followed since that time. Control of the disease had been poor. She rarely tested her own urine and in 1935 was in coma. In 1927 or 1928 an erythematous plaquelike scaling eruption developed on the dorsa of both feet. She thought that this had appeared at sites of irritation caused by her shoes. Shortly after this eruption appeared, a similar lesion developed on the anterior tibial surface of the right leg, just below the knee. The lesions were not itching or weeping but gradually spread at their peripheries. A variety of local treatments, including use of ultraviolet light, had been tried, without relief.

General physical examination gave essentially negative results. The concentration of hemoglobin and the numbers of erythrocytes and leukocytes were within normal limits; blood flocculation tests gave negative results, and the basal metabolic rate was —14 per cent.

On examination of the skin, regions of glazed, dry, scaling skin were found on the dorsa of both feet and on the right anterior tibial surface. A diagnosis of necrobiosis lipoidica diabeticorum was made on the clinical appearance alone, because the patient refused a biopsy.

Grossly, the vessels of the extremities were open, and the capillaries were normal. Funduscopic examination, however, revealed numerous scattered large and small punctate hemorrhages in the retina with relatively few exudates of the central punctate diabetic type, but cotton-wool exudates were present in a number of places. The veins of the retina were full and the arteries mildly narrowed, but there was no definite sclerosis.

Determination of the values for blood lipoids gave essentially normal results; cholesterol, 200 mg. and 241 mg. per hundred cubic centimeters on two separate occasions; cholesterol esters, 144 mg. per hundred cubic centimeters; lecithin, 245 mg. per hundred cubic centimeters; fatty acids, 322 mg. per hundred cubic centimeters, and total lipoids, 522 mg., per hundred cubic centimeters.

The value for blood sugar on admission was 280 mg. per hundred cubic centimeters, and the urine contained 23.8 Gm. of sugar in a twenty-four hour sample; tests for acetone and diacetic acid gave positive results. With a diet of 104 Gm. of carbohydrates, 62 Gm. of protein and 89 Gm. of fat plus 40 units of protamine zinc insulin every morning, the glycosuria rapidly disappeared. The patient was sent home on this regimen.

CASE 2.—A Polish woman aged 43 was first seen at the clinic in August 1937. A family history of diabetes mellitus was not obtainable. The cutaneous lesions had developed prior to the onset of diabetes. Four brownish plaques, one on each calf, one on the right ankle and one on the left wrist, developed within one month in 1935 and slowly became enlarged during the next two years. Local treatment was without success, and the patient suffered somewhat from itching and burning of the lesions. However, the diabetes had not been diagnosed before she came to the clinic. At that time the patient had acidosis with a blood sugar level of 349 mg. per hundred cubic centimeters and 33.07 Gm. of sugar in a twenty-four hour specimen of urine; tests for acetone and diacetic acid gave positive results.

Except for the cutaneous lesions and changes in the eyegrounds, general physical examination gave essentially negative results. On the left wrist, on both calves and on the right ankle were roughly circinate, well defined, smooth, waxy, slightly elevated brownish plaques. These were firm and not tender and showed central scarring and telangiectasia. Biopsy of one lesion showed the typical histologic picture of necrobiosis lipoidica diabeticorum.

Funduscopic examination showed only an exaggerated light reflex on the part of the retinal arteries, but not actual sclerosis; a few white dots were also present in the retina.

Studies of the blood lipoids revealed essentially normal values throughout, as follows: cholesterol, 248 mg. per hundred cubic centimeters on one occasion and 189 mg. per hundred cubic centimeters on another, five days later; cholesterol esters, 120 mg. per hundred cubic centimeters; lecithin, 227 mg. per hundred cubic centimeters; fatty acids, 402 mg. per hundred cubic centimeters on admission and 303 mg. per hundred cubic centimeters five days later; total lipoids, 650 mg. per hundred cubic centimeters on admission and 492 mg. per hundred cubic centimeters five days later.

The glycosuria was readily controlled by a weighed diet and by the administration of 30 units of protamine zinc insulin and 25 units of crystalline (Lilly) insulin every morning, but during her stay at the clinic (ten days), change in the cutaneous lesions was not observed.

CASE 3.—A white Canadian woman aged 29 was first seen at the clinic in June 1938. She did not give a family history of diabetes. The cutaneous lesions had developed about four months after the first appearance of the symptoms of diabetes mellitus, although the latter was not diagnosed until about seven months after that time. In May 1935 malaise and weakness first developed; the condition was diagnosed as adenoma of the thyroid without hyperthyroidism. Urinalysis at that time gave normal results.

In November the patient became pregnant. She did not gain weight during the pregnancy, but in January 1936 she actually began to lose weight; mild polyuria, polydipsia, polyphagia and pruritus vulvae developed. However, then, as throughout her pregnancy, urinalysis at intervals were reported as giving negative results.

In April, firm, yellowish subcutaneous plaques appeared on the dorsa of the feet and gradually increased in size. These were never painful and never ulcerated. In July the patient bruised her left leg (on the lower part of the anterior tibial surface), and a similar plaque appeared at the site of the injury. About the same time she gave birth at term to a stillborn child. It is of interest to note that during the last trimester of pregnancy the symptoms of diabetes practically disappeared and that they did not recur to any marked degree after delivery. It was not until just after a thyroidectomy, in November, that glycosuria was discovered.

She was given a weighed diet, and 10 units of unmodified insulin was administered every morning and evening. The patient's attitude toward her condition was one of indifference; she rarely tested her own urine. The cutaneous lesions did not increase or decrease in size after the institution of insulin therapy. In June 1937, 30 units of protamine zinc insulin was given every morning.

The findings on general physical examination were essentially normal. The concentration of hemoglobin and the numbers of erythrocytes and leukocytes were normal; blood flocculation was normal, and the basal metabolic rate was +9 per cent. The results of funduscopic examination were negative, and the vessels of the extremities were open. Examination of the skin revealed on the dorsa of the feet and on the anterior tibial surface of the left leg elevated, firm, well defined yellow-centered plaques which had reddish brown borders and a fine plexus of veins on the surface. The patient refused a biopsy.

In this case also the values for the blood lipoids were entirely within normal limits, cholesterol, 187 mg.; cholesterol esters, 132 mg.; lecithin, 212 mg.; fatty acids, 361 mg., and total lipoids, 548 mg., per hundred cubic centimeters.

The patient was sent home after being instructed to take a diet free of animal fat and with a low content of phosphorus plus 20 units of protamine zinc insulin and 10 units of Lilly crystalline insulin every morning. Several months later she reported no improvement in the lesions.

CASE 4.—A white American woman aged 27 was first seen at the clinic in August 1938. She did not give a family history of diabetes. The patient had diabetes which dated back to 1929; at that time the classic symptoms of diabetes suddenly developed, and glycosuria was found. She was given a weighed diet, and 50 units of unmodified insulin was administered twice daily. She followed this program for one year, then changed to a qualitative diet, 20 units of unmodified insulin being administered three times daily. On this regimen control of the disease was very irregular. She had frequent insulin reactions and was in a state of diabetic coma twice.

In 1932 several small reddish regions appeared on the anterior tibial surfaces of the legs and on the dorsa of the feet. Each of these lesions ran an asymptomatic course of about six weeks. During the first half of this period the lesions increased gradually and slightly in size, then gradually receded, leaving depressed scars. During the next six years several such lesions at the same sites appeared and went through the same cycle. Two or three months prior to her registration at the clinic one of these lesions developed over the external malleolus of the left ankle and gradually increased in size.

Physical examination revealed in addition to the cutaneous lesions: (1) bilateral cystic mastitis, (2) an apical systolic murmur and (3) a retroverted uterus with prolapse of the adnexa. The blood was normal, and blood flocculation was normal. Roentgen examination of the thorax gave negative results. Funduscopic examination revealed nothing of importance, and the vessels of the extremities were open. Examination of the skin showed a brownish plaque just above the left external malleolus plus several depressed scars over the anterior tibial surfaces. The patient refused a biopsy.

In this case, also, the values for blood lipoids were normal, being estimated as follows: cholesterol, 203 mg.; cholesterol esters, 132 mg.; lecithin, 227 mg.; fatty acids, 295 mg., and total lipoids, 498 mg., per hundred cubic centimeters.

The patient responded well to a diet (basal plus 50 per cent) and was sent home with instructions to use 30 units of protamine zinc insulin and 10 units of crystalline insulin every morning plus 10 units of crystalline insulin every evening.

Case 5.—A white American girl aged 14 years was first seen at the clinic in October 1928, at the age of 5 years. She complained of lifelong enuresis and of failure to gain weight. Glycosuria had been observed elsewhere one week prior to her registration at the clinic, and she had been given a qualitative diet.

Physical examination at that time disclosed no evidence of active infection in the upper portion of the respiratory tract; roentgen examination of the thorax gave negative results, although the patient had been having frequent colds. The urine was free of sugar, but the value for blood sugar was 200 mg. per hundred

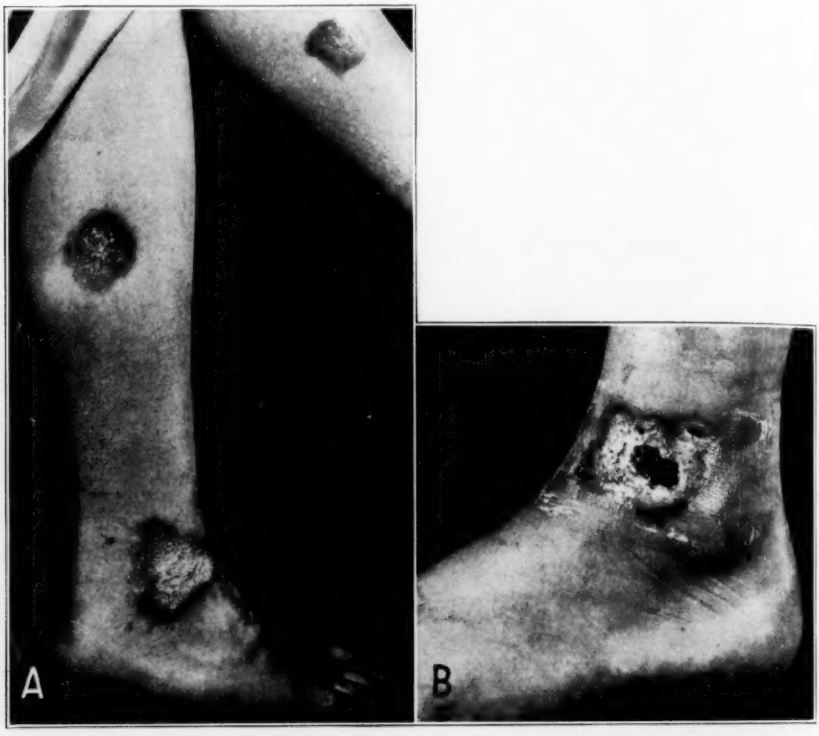

Fig. 1.—*A*, necrobiosis lipoidica diabeticorum, with multicolored hypertrophic and atrophic scaling plaques. *B*, necrobiosis lipoidica diabeticorum. Note the large plaque which is yellow with reddish blue borders and central ulceration.

cubic centimeters on admission. The blood was normal, and flocculation tests gave negative results. Study of the blood lipoids was not made at that time. The girl was sent home after being instructed as to a weighed diet and was directed to take 2 units of unmodified insulin twice daily.

She gradually increased the diet and the dose of insulin over the next nine years until she was taking 25 units of the unmodified insulin twice daily. For two years prior to her second registration at the clinic, in 1938, she had been

receiving 50 units of protamine zinc insulin every morning. Her cooperation as regards diet was poor, however, and in 1934 she was in diabetic coma for several hours. Together with the poorly controlled diabetes, there had been delayed puberty; she had never menstruated up to the time when she was seen in 1938.

The first cutaneous lesion appeared on the lower part of the left leg in 1930. It was a yellowish plaque which ulcerated soon after its development and then slowly healed within a month. The patient had no further cutaneous lesions until 1936, when plaques similar to the first began developing, one after the other, on the lower parts of both legs and on the anterior surface of the right thigh.

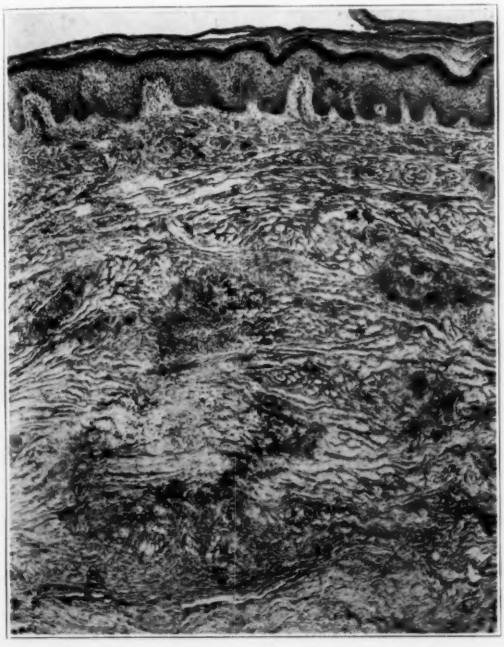

Fig. 2.—Necrobiosis lipoidica diabeticorum. A region of pseudonecrosis is present in the cutis, surrounded by extracellular deposits of lipoids that appear as black granules. A mild inflammatory reaction is present, as is evident by infiltration of lymphocytes and leukocytes around the regions of necrosis. Sudan III stain.

Several weeks prior to her second registration, an ulcerated lesion developed on the lateral surface of the left ankle, which persisted (fig. 1).

On physical examination at the time of her registration the patient was poorly developed but in good general health otherwise. The blood was normal, blood flocculation gave negative results and roentgen examination of the thorax gave negative results. Funduscopic examination also gave negative results, and the vessels of the extremities were open.

Examination of the skin showed: (1) on the lateral aspects of the left ankle a large punched-out ulcer, surrounded by a raised, rolled border; (2) on the lateral

aspect of the right ankle a large erythematous, scaling lesion, and (3) on the lower portion of both legs and on the anterior surface of the right thigh a few infiltrated, dense plaques of definite yellowish hue, crossed superficially by delicate blood vessels. The mucosa of both the soft palate and the eyelids had a definite yellowish hue. Biopsy of the yellowish plaques showed the typical histologic picture of necrobiosis lipoidica diabeticorum (fig. 2).

Quantitative determinations of the lipoid constituents of both the blood and the cutaneous lesions were made. As has already been pointed out, the value for tissue lecithin was high in this case. None of the values for blood lipoids were markedly elevated, although the fatty acids and the total lipoids were sufficiently greater than normal to make them worthy of note, 500 mg. and 728 mg. per hundred cubic centimeters respectively. The value for blood cholesterol was 228 mg., that for cholesterol esters 177 mg., and that for lecithin 250 mg., per hundred cubic centimeters.

The patient was sent home after receiving instruction as to a weighed diet of relatively low animal fat content and was directed to use 60 units of protamine zinc insulin and 45 units of crystalline insulin every morning. When last heard from, in September, she reported that the lesions were about the same as they had been in June.

CASE 6.—A white American woman aged 61 was first seen at the clinic in November 1938. A family history of diabetes was not elicited. She stated that she had repeatedly had lesions on the lower portion of both legs, which occurred singly or in crops, as reddish papules, during the preceding two or three years. Each of these lesions persisted for three or four weeks, during which time they first increased a little in size and then gradually faded, to leave depressed scars covered with fine scales. A salve had been used in treatment at home. The lesions were never painful and never became ulcerated. During May and June she was incapacitated with two slowly healing, somewhat painful ulcers on the left foot. Under treatment with a salve and a pressure bandage these lesions finally cleared up, and depressed scars remained. Because the patient failed to regain strength after this time, a urinalysis was finally done, in August, and glycosuria was discovered. She had had none of the classic symptoms of diabetes mellitus. She was given a weighed diet, and 30 units of protamine zinc insulin was taken every morning, a program which only she, of all our patients, carefully followed. She also had been taking compound solution of iodine U. S. P., 10 to 15 drops three times a day, since August, because at that time a basal metabolic rate of + 44 per cent had been discovered.

In September the patient first began having pains in both calves, and in October she again had ulcerated lesions on the left foot and leg. At about the same time she began to notice numbness, burning and tingling of the legs. A wide variety of local treatments for the ulcer failed to relieve the pain and did not cause healing of the ulcers.

On admission a small thyroid adenoma was present, but tremor or other evidence of hyperthyroidism was not found, except for a basal metabolic rate of + 30 per cent. Treatment with compound solution of iodine was not continued, however. The blood was normal, and blood flocculation gave negative results.

Examination of the vessels of the extremities revealed no pulsations and no oscillometric deviations below the knees on either side. Roentgen studies of the lower extremities showed slight calcification in the proximal vessels of the left foot. Narrowing of the retinal vessels, grade 1 (on a basis of 1 to 4) was present, and sclerosis grade 1 (of the chronic hypertensive type) was noted, plus several small

punctate hemorrhages of the diabetic type around the left macular region. The right retina was slightly detached in the temporal zone.

Examination of the skin revealed an ulcerated lesion between the fourth and fifth toes of the left foot, similar to the superficial pyoderma sometimes found in association with diabetes. Cultures of material from this ulcer on the ordinary mediums yielded gram-positive cocci. There was also an ulcerated region measuring 1 by 2 cm., covered with a small black scab, on the medial side of the dorsum of the left foot. This was diagnosed as necrobiosis lipoidica diabeticorum.

Two studies of the blood lipoids were made, two days apart. Neither revealed any significant changes. The first showed the value for cholesterol to be 238 mg., that for cholesterol esters 155 mg., that for lecithin 230 mg., that for fatty acids 350 mg. and that for total lipoids 585 mg. per hundred cubic centimeters. The second showed the value for cholesterol to be 222 mg., that for fatty acids 314 mg., and that for total lipoids, 536 mg., per hundred cubic centimeters.

Despite control of the glycosuria by means of a weighed diet and a proper amount of insulin, excruciating pain in the left leg and foot continued unabated. Local application of 2 per cent procaine and nupercaine ointment to the lesion between the toes of the left foot gave no relief from the pain, nor did either lesion show any tendency toward healing. After ten days of rest in bed and potassium permanganate soaks to the foot, when redness and swelling of the dorsum of the foot appeared, amputation of the left leg just below the knee was performed. A prophylactic dose of combined gas gangrene and tetanus antitoxin was given preoperatively. On the second postoperative day acidosis reappeared, and examination of the stump showed crepitation, which rapidly extended proximally. Amputation at the midthigh was immediately performed, and postoperatively several doses of the combined antitoxin (more than 100,000 units) were given. These had to be accompanied by histamine administered subcutaneously because of a severe asthmatic reaction to the first dose of the serum. Increased doses of both protamine and crystalline insulin served to control the acidosis within twenty-four hours after it had begun. However, toxicity progressed, and the patient died on the fifth postoperative day.

Microscopic studies were made not only of the necrobiotic lesions on the amputated leg but of the arteries and long nerves. The lesion itself was one of necrobiosis lipoidica. The vessels stained with both hematoxylin and eosin, and fat stains (sudan III) showed intimal proliferation. In the regions of proliferation fat particles were present. Weigert stains of the nerves showed degeneration. It will be remembered that this patient had suffered from extreme pain in that leg. This, as microscopic studies showed, might have been on the basis of poor circulation or neuritis.

Case 7.—An American woman aged 52 was first seen at the clinic in November 1938. She did not give a family history of diabetes. Classic symptoms of diabetes mellitus had developed in 1936, but it was not until 1937 that she was given a qualitative diet and was instructed to take 25 units of unmodified insulin every morning and evening. Control of the disease had been very irregular, and since August she had experienced symptoms of acidosis, including abdominal pains, nausea, vomiting and malaise on repeated occasions. She had lost 50 pounds (23 Kg.) since then. Almost since the onset of the diabetes she had noticed repeatedly a single papular lesion on the lower portion of each leg, each of which appeared and faded within one or two weeks. The latest one had developed on the left anterior tibial surface three weeks prior to registration at the clinic, and this lesion had become ulcerated.

Physical examination revealed evidence of acidosis, including acetone breath, air hunger, hot, dry skin, glycosuria grade 4 (on the basis of 1 to 4), acetone and diacetic acid in the urine and a blood sugar level of 338 mg. per hundred cubic centimeters; a thin vaginal discharge, which she had had for one year; ready bleeding of the cervix on examination, and an aortic systolic murmur and thrill, although roentgenoscopic examination failed to reveal calcification of the aortic valve. The blood was normal, and the Wassermann reaction of the blood was negative, although both the Kline and the Kahn tests gave positive results. Dilatation, curettage and cervical biopsy revealed no malignant disease. Roentgenoscopic examination of the thorax gave negative results, and the vessels of the extremities were open. Examination of the skin showed a crusted, well circumscribed lesion, 1 by 2 cm., on the lateral surface of the left ankle. Clinically this was considered necrobiosis lipoidica diabeticorum, although a biopsy was not performed. All the values for blood lipoids were low, ranging as follows: cholesterol, 137 mg., cholesterol esters, 87 mg., lecithin, 192 mg., fatty acids, 270 mg., and total lipoids, 401 mg., per hundred cubic centimeters.

The glycosuria rapidly cleared after a weighed diet was prescribed in addition to a combination of protamine zinc and crystalline insulin, but the lesions failed to change in the two weeks during which the patient was hospitalized here.

CASE 8.—A white American man aged 27 was first seen at the clinic in August 1939. He did not give a family history of diabetes. Classic symptoms of diabetes mellitus had developed in 1935. At that time the concentration of blood sugar was 375 mg. per hundred cubic centimeters. He was given a quantitative diet and 30 to 40 units of unmodified insulin daily. One year later he began a qualitative type of diet which he had followed since that time. Also, in the last year, he had been using 30 units of protamine zinc insulin plus 10 units of unmodified insulin daily instead of the unmodified insulin alone. On the whole, his control of the disease had been poor. He tested his urine only once a week, and then it was always "heavy with sugar." The concentration of blood sugar varied from 180 to 375 mg. per hundred cubic centimeters. However, he had never been in coma and had not experienced insulin reactions. For one and a half years he had had some pains in both legs plus burning and tingling in the feet.

In 1936 a small area of redness appeared on the right shin and gradually became enlarged. Similar lesions appeared around this first one, and as they all became enlarged they coalesced to form a slowly enlarging, red, dry, scaling irregular plaque over the right anterior tibial region. In 1938 a similar lesion appeared on the left calf, and six months later one appeared on the left tibial region. The last-mentioned lesion progressed rapidly. The lesions were tender, especially at their borders. The patient had had various types of treatment for the cutaneous lesions, including eight treatments with roentgen rays to the lesion on the right leg and one treatment with roentgen rays to the lesion on the left leg. General physical examination gave essentially negative results. The concentration of hemoglobin was normal, and the blood flocculation test gave negative results. Examination of the vessels of the extremities revealed nothing significant. The patient did not remain long enough to permit a funduscopic examination. Examination of the skin showed on the anterior surface of the lower part of the right leg an irregular, slightly raised reddish plaque with an advancing telangiectatic border and a dry, scaling center which was slightly depressed; the lesion measured 8 inches (20 cm.). Biopsy of this lesion showed the typical histopathologic picture. Similar lesions were present on the lower part of the left leg and on the left calf.

Fig. 3.—Typical appearance of the lesions of necrobiosis lipoidica diabeticorum. Note the multiplicity of colors and the yellowish red center.

The values for blood lipoids were entirely within normal limits, being estimated as follows: cholesterol, 208 mg.; cholesterol esters, 118 mg.; lecithin, 171 mg.; fatty acids, 269 mg., and total lipoids, 477 mg., per hundred cubic centimeters. The value for blood sugar on admission was 323 mg. per hundred cubic centimeters. Analysis of the necrobiotic lesions quantitatively revealed the figures already given, namely, cholesterol, 0.3 per cent; cholesterol esters, 0.2 per cent; lecithin, 1.1 per cent; total fatty acids, 13.4 per cent, and total lipoids, 13.6 per cent, of the wet weight of the specimen. We have obtained a colored photograph of the lesions in this case (fig. 3).

SUMMARY

Seventy-eight cases of necrobiosis lipoidica diabeticorum which have been described in the literature since the first report of this dermatosis by Oppenheim, in 1929, are reviewed. Observations on 8 cases of necrobiosis lipoidica diabeticorum encountered at the Mayo Clinic since 1936 are related. More than 87 per cent of all the patients, both those seen elsewhere and those seen at the clinic, had diabetes mellitus, and in 8 typical cases of necrobiosis evidence of diabetes mellitus was not found. In the majority of the cases in the entire series the cutaneous lesions had developed several months to as long as seventeen years after the onset of diabetes, although in about 18 per cent of the cases encountered elsewhere and 25 per cent of those encountered at the clinic the reverse was true, the cutaneous lesions preceding the onset of the diabetes by as long as eight years. All patients were white, and more than 80 per cent were women. The commonest age of onset among all patients was between 10 and 40 years. In those who had diabetes mellitus, the constitutional disease in most instances could be called moderately severe to severe, and in most of them the diabetes had been poorly controlled. Trauma apparently played a definite role in the development of the cutaneous lesions in several cases.

The lesions in this condition are most often reddish papules or yellowish plaques with well defined reddish brown borders, much infiltration and central telangiectasia. They usually occur on the lower parts of the legs. Microscopically the lesions are characterized by changes in the deep layers of the cutis, consisting of necrobiotic regions in which there are granular degeneration of the collagen fibers, loss of elastic fibers and extracellular deposition of various lipoids, surrounded by a region in which the arterioles show intimal proliferation and perivascular monocytic infiltration. The absence of xanthoma or foam cells containing cholesterol and cholesterol esters differentiates these lesions from those of the other xanthomatoses except lipoid proteinosis, which represents a different clinical picture. Quantitative determinations of the lipoid constituents of these lesions were suggestive of a relative increase of lecithin in the tissues.

Studies of the blood lipoids have shown that in the majority of all cases encountered elsewhere and in all of the cases encountered at the

clinic the values lay within normal limits. The lesions tended to run a chronic course, and neither local therapy nor, in the case of diabetics, general management tended to speed their healing. In some cases the lesions slowly receded and left depressed scars.

Two ideas regarding the pathogenesis of this condition have been considered: (1) that which assumes the occurrence of a primary vascular injury, possibly by circulating toxins, with secondary thrombosis, necrosis, and fat imbibition and (2) that which assumes a local lipoid disturbance in the skin, based on a general disturbance in fat metabolism. Neither hypothesis has proved satisfactory in the light of studies made both here and elsewhere. Therefore, the pathogenesis of this condition remains obscure.

BANTI SYNDROME (FIBROCONGESTIVE SPLENOMEGALY)

DEFINITION, CLASSIFICATION AND PATHOGENESIS

PAOLO RAVENNA, M.D.
CHICAGO

The Banti syndrome is still an unsolved problem. The question of cardinal importance is whether the splenomegaly is primary or secondary to portal or hepatic changes.

Banti [1] stated the belief that the trouble lay primarily in the spleen and that the portal and hepatic changes were dependent on the splenic ones. The idea that the splenomegaly was the consequence of circulatory disturbances was put forward by Dock and Warthin [2] and further developed with the description of the thrombophlebitic splenomegaly.[3] This theory occupied a position of definite advantage when it was recognized that the structure of Banti splenomegaly was chiefly congestive [4] and that

1. Banti, G.: La splenomegalia con cirrosi epatica, Sperimentale (sez. biol.) **48**:407, 1894; La splénomégalie avec cirrhose du foie, Semaine méd. **14**:318, 1894; Ueber Morbus Banti, Folia haemat. **10**:33, 1910.

2. Dock, G., and Warthin, A. S.: A Clinical and Pathological Study of Two Cases of Splenic Anaemia, with Early and Late Stages of Cirrhosis, Am. J. M. Sc. **127**:24, 1904.

3. (*a*) Cauchois, A.: Splénomégalies chroniques d'origine pyléthrombosique, Thesis, Paris, no. 422, Paris, G. Steinheil, 1908. (*b*) Dévé, F.: Splénomégalie chronique avec anémie d'origine pyléthrombosique, Normandie méd. **23**:109 (March) 1908. (*c*) Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anaemia and Banti's Disease, Internat. Clin. **4**:189, 1910. (*d*) Eppinger, H.: Hepato-lienale Erkrankungen, Berlin, Julius Springer, 1920. (*e*) Frugoni, C.: La splenomegalia tromboflebitica primitiva, Arch. di pat. e clin. med. **3**:574 (Dec.) 1924; La splénomégalie thrombophlébitique, Rev. belge sc. méd. **10**:227 (April) 1938. (*f*) Ceconi, A.: La splenomegalia tromboflebitica, Gazz. d. osp. **50**:265 (March 3) 1929. (*g*) Klemperer, P.: Cavernomatous Transformation of the Portal Vein, Arch. Path. **6**:353 (Sept.) 1928.

4. (*a*) Greppi, E.: Il tumore di milza contrattile emorragiparo come probabile forma di splenoangiopatia primitiva, Minerva med. **2**:644 (Sept. 22) 1928; Die contractile Milztumor und seine Beziehungen zur thrombophlebitischen Splenomegalie, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**:615, 1928. (*b*) Villa, L.: Il significato semiologico della contrazione di volume della milza mediante adrenalina par la diagnosi delle splenomegalie voluminose, Boll. d. soc. med.-chir., Pavia **3**:479, 1928; Cuore e circolaz. **12**:465, 1928. (*c*) Larrabee, R. C.: Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, Am. J. M. Sc. **188**:745 (Dec.) 1934. (*d*) Rousselot, L. M.: The Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome, J. A. M. A. **107**:1788 (Nov. 28) 1936.

the pressure in the splenic vein was highly increased.[5] But these same signs of portal hypertension were found to be present when an obstructive factor was missing. This fact was responsible for the widest gap in the support of the theory of venous congestion as the causative agent and formed an apparent paradox of great interest.[6]

It is my opinion, however, that this apparent contradiction may be explained if the portal congestion is considered to be the effect of an increased flow of blood into the spleen ("primary acute congestion"). In 1936 I published a detailed study[7] in which I suggested this interpretation. I believe that some important recent contributions by other observers and my successive experience have brought further evidence to the support of this view.

The object of this paper is to correlate these various arguments, thus bringing up to date an idea which may have some bearing both on the understanding of the physiology of the spleen and on the clinical management of its circulatory dysfunctions. Before proceeding, it seems advisable to suggest a definition and a scheme of classification of the Banti splenomegalies; these preliminary considerations should be constantly borne in mind, as they form the premises of any discussion on the pathogenesis of the syndrome.

DEFINITION

Banti's conception of a symptom complex which is dominated by chronic splenomegaly, characterized by certain particular anatomicohistologic changes, due to an unknown agent and recognizable as a separate, clearcut disease can no longer be maintained. Many conditions presenting the clinical and pathologic features described by Banti have been shown to be dependent on various known causative agents.[8] The term "Banti's disease" has thus been discarded and "the Banti syndrome" used in its place, though even recently an author,[8'] with

5. Thompson, W. P.; Caughey, J. L.; Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), J. Clin. Investigation **16**:571 (July) 1937.

6. (*a*) Whipple, A. O.: The Combined Spleen Clinic, Surg., Gynec. & Obst. **64**:296 (Feb.) 1937; (*b*) The Medico-Surgical Splenopathies: Introduction, Bull. New York Acad. Med. **15**:174 (March) 1939. (*c*) Rousselot, L. M.: Congestive Splenomegaly, ibid. **15**:188 (March) 1939.

7. Ravenna, P.: La splenomegalia fibroso-congestizia primitiva con cirrosi epatica e la sua sistemazione fra le sindromi bantiane, Minerva med. **1**:225 (March 10); 255 (March 17); 276 (March 24); 306 (March 31) 1936.

8. (*a*) Micheli, F.: Contributo clinico ed anatomopatologico allo studio della varietà luetica del morbo di Banti, Soc. ital. per il progr. delle sc. **7**:962, 1913. (*b*) Dürr, R.: Bantimilz und hepatolienale Fibrose, Beitr. z. path. Anat. u. z. allg. Path. **74**:418, 1924.

8'. Patrassi, G.: Il morbo di Banti inteso come cirrosi splenomegalica a decorso protratto, Arch. per le sc. med. **69**:259 (April) 1940.

remarkable lack of criticism, insisted on the term Banti's disease, in spite of the fact that he admitted the multiple etiologic considerations. Even the idea of a Banti syndrome has been the object of repeated criticisms until recently.

It must be granted, however, that chronic splenomegalies not related to any typical disease of the blood, to intrasplenic deposits of lipoids or to tumors are a matter of universal experience, though their existence has been noted more often in certain countries than in others. Banti [1] and several other Italian authors [9] emphasized that this type of splenic enlargement is more or less frequently associated with hepatic cirrhosis. As to the relation between splenomegaly and cirrhosis, it was noted that the same degrees of splenic enlargement are found without any lesion of the liver, or with diverse stages of typical cirrhosis. There was enough evidence, it was believed, to warrant the assumption that this splenomegaly is either autonomous or coordinated with, but not dependent on, the hepatic lesion.

This intimate relation between splenomegaly and cirrhosis of the liver, in which the splenic enlargement constitutes, apparently at least, the primary lesion, forms the basis of the modern idea of the Banti syndrome.[10] To the Banti syndrome can therefore be ascribed the conditions in which the morbid picture is dominated by a considerable chronic splenic enlargement, nonhemolytic anemia and leukopenia. The clinical course is often punctuated by repeated severe hematemeses and sometimes by transitory or permanent ascites. More or less constantly these symptoms are coupled with cirrhosis of the liver. Splenomegalies due to diseases of the blood, to intrasplenic deposit of lipoids or to tumors must not be confounded with Banti syndrome. Splenic anemia, a term which from Griesinger's times up to recent years [11] has pooled all these and other various morbid conditions, is really void of any particular meaning.[12] Almost all chronic splenomegalies are, in point of fact, associated with such a type of anemia.

9. (*a*) Micheli, F.: Sul morbo di Banti, Arch. per le sc. med **33**:351, 461 and 495, 1909; Sistemazione e patologia delle splenomegalie primitive, Turin, Unione tipografico editrice torinese, 1910. (*b*) de Vecchi, B., and Zanotti, P.: Su di una particolare splenomegalia primitiva, Sperimentale, Arch. di biol. **82**:217, 1928.

10. (*a*) Greppi, E.: La maladie de Banti. Evolution et état actuel du problème, Rev. belge sc. méd. **10**:237 (April) 1938. (*b*) Ravenna.[7]

11. Hanrahan, E. M.: Splenic Anemia: A Study of End Results With and Without Splenectomy Based on Thirty-Five Cases, Arch. Surg. **10**:639 (March) 1925. Mayo, W. J.: Certain Blood Dyscrasias Dependent on Pathologic Conditions of the Spleen, J. A. M. A. **88**:815 (Sept. 13) 1924.

12. (*a*) Naegeli, P.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931, p. 560. (*b*) Klemperer, P.: The Pathologic Anatomy of Splenomegaly, Am. J. Clin. Path. **6**:99 (March) 1936; The Spleen, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, pp. 1591-1728.

CLASSIFICATION

Actual classifications are mainly founded on morphologic bases. Macroscopic and histologic examinations have decided whether the splenomegaly had to be classified as fibrous or fibroadenic,[1] congestive [4] or siderotic.[13] Naegeli's [12] and McNee's [14] classifications were based on which tissue was prevalently damaged. The concomitant presence of hepatic cirrhosis or of thrombophlebitis gave rise to other classes (Eppinger [3d] and Rousselot [6c]). All these classes do not differentiate nosologic entities but merely point to characteristics and courses which may depend either on the same or on different causative agents.

In syphilitic patients with the Banti syndrome, for instance, all the aforementioned aspects have been recorded (Micheli [8a] and Minot [15]), either with or without histologic signs of syphilis (Ravenna [7]). The only correct diagnosis would be that of Banti syndrome of syphilitic origin, which offers a comprehensive definition of the disease and not only one particular aspect.

One of the best schemes for classification was suggested by Klemperer,[12b] and it was based on pathogenetic criteria. But a lasting classification should be based on the etiology. Only conditions of which the cause is not determined may be divided, somewhat arbitrarily, from the standpoint of morphologic aspects. It would then be correct to make a diagnosis of primary or cryptogenetic splenomegaly with prevailing congestion (hemorrhages or siderosis) or with prevailing fibrosis (fibroadenia or cirrhosis). The latter class evidently includes instances presenting all the etiologic and morphologic characters described by Banti, and it therefore may conserve the name of Banti's disease.

The following scheme may be suitable for a simple classification.

A. Of known origin	infective	syphilis leishmaniasis schistosomiasis malaria tuberculosis
	toxic	alcohol lead phosphorus
B. Of undetermined origin (primary fibrocongestive splenomegaly with cirrhosis)	with prevailing congestion	
	with prevailing fibrosis (Banti's disease)	

13. Gamna, C.: Contributo alla conoscenza della splenomegalia primitiva, Haematologica **4**:129, 1923.

14. McNee, J. W.: The Spleen: Its Structure, Function and Diseases, Lancet **1**:951 (May 2); 1009 (May 9); 1063 (May 16) 1931.

The progress of the general knowledge of etiology will enlarge class A, with the inclusion of other causative agents, while the number of cases ascribed to class B is bound to decrease and ultimately disappear.

CLINICAL AND PATHOLOGIC NOTES

For a long time great importance was attributed to the anemia which almost constantly accompanies Banti's syndrome. It is of moderate degree, normocytic and nonhemolytic and is associated with well marked leukopenia, relative or absolute monocytosis, and frequently with decrease of blood platelets. Its significance decreased considerably when it was generally recognized that this type of anemia, as pointed out by Micheli in 1903,[16] is usually associated with any considerable splenic enlargement, from whatever cause.

Lately attention has been drawn to a condition of splenic and portal congestion of high degree, and it has been noted that, being less considerable or absent in splenomegalies from other causes, this congestion forms a salient and typical feature of Banti splenomegalies. Its presence is inferred from (*1*) the pronounced decrease of splenic volume after injection of epinephrine [17] or after hemorrhage; (*2*) the frequent occurrence of copious hemorrhages from the gastrointestinal tract; (*3*) the frequency of transitory or permanent ascites, and (*4*) the hypertension in the splenic veins, as determined during surgical intervention.[5]

The spleen is invariably greatly enlarged but shows no specific characteristics, and this fact accounts for the long opposition that Banti's idea met with when morphologic criteria were dominating morbid anatomy as well as clinical diagnostics. A certain similarity of lesions, however, was noted, consisting in connective and elastic hyperplasia of the capsule and trabeculae and fibrosis and hyperplasia of the reticular framework of the splenic pulp. The liver is normal in some instances but mostly presents various degrees of Laennec's cirrhosis. Moreover, careful examination showed many definite signs of portal congestion, represented by (*1*) the gross and histologic aspect of the spleen: dilatation of the sinuses, intrasplenic hemorrhages and their residuals and the siderotic nodules [18]; (*2*) the dilatation of small vessels inside the spleen,

15. Minot, G. R.: Anemias, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1932, vol. 2, p. 642.

16. Micheli, F.: Note ematologiche sulla malattia di Banti, Riv. di clin. med. **4**:65 (May); 81 (June); 97 (July) 1903.

17. Greppi.[4a] Villa.[4b]

18. B. de Vecchi, B. Picchi and G. Patrassi (Ricerche sistematiche sulla genesi e sul valore delle lesioni spleniche conosciute col nome di aree di Gamna, Arch. di pat. e clin. med. **8**:17 [Jan.] 1929) and C. Oberling (Le rôle pathogène de la mycose splénique de Nanta, Presse méd. **36**:2 [Jan. 4] 1928), examining some of Banti's own slides, observed siderotic nodules also in his original cases.

of the splenic veins and its roots and of portal and mesenteric veins,[19] and (*3*) the dilatation of collateral portal-general paths of circulation. The aforementioned frequence of gastroesophageal hemorrhages and ascites is, of course, a pathologic as well as a clinical sign of portal congestion.

Pathologists usually evaluate the state of congestion from the anatomic aspect of the spleen removed surgically or at necropsy. This criterion is misleading, as the spleen is larger during life than after death and is subject to shrinkage as an effect of various operative procedures, of anesthetics (both ether and chloroform) and of epinephrine, which is often purposely given. A further amount of blood flows out of the splenic tract of resected veins. That is possibly the reason why the presence of congestion had been so long overlooked by pathologists and by Banti himself. But, once recognized, the importance of splenic and portal hypertension was stressed increasingly.[20] Some authors[21] have used the term congestive splenomegaly as synonymous with Banti's syndrome. Piney[22] wrote: "There seems to be little doubt that Banti's disease is essentially a pathological state of the vascular system of the spleen;" and Greppi[23] noted that the vascular factor was becoming the "Leit-motif" of splenic pathology.

Thrombosis of the splenic and portal veins, their cavernomatous transformation and their stenosis by external compression due to various causes or various stages of hepatic cirrhosis were often noted and referred to as possible or probable causes of the splenic and portal congestion. Experimentally, however, attempts to produce chronic splenomegaly by means of varied derangements in the portal or splenic circulation have been uniformly disappointing.[23a] Only Rousselot and Thomson[23b] have claimed positive results; obviously, their experiments must be confirmed independently before definite conclusions be drawn.

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19. McMichael, J.: The Pathology of Hepatolienal Fibrosis, J. Path. & Bact. **39**:481, 1934. Rousselot.[6c]

20. (*a*) Villa, L.: Sulla retrattilità splenica, Rassegna med. **15**:127 (Sept. 30) 1935. (*b*) McNee, J. W.: Croonian Lectures on Liver and Spleen: Their Clinical and Pathological Associations, Brit. M. J. **1**:1017 (June 4); 1068 (June 11); 1111 (June 18) 1932. McMichael.[19]

21. Greppi.[4a] Larrabee.[4c] Rousselot.[4d]

22. Piney, A.: Recent Advances in Haematology, ed. 4, London, J. & A. Churchill, Ltd., 1939, p. 294.

23. Greppi, E.: Morbo di Banti 1938, Riv. di clin. med. **40**:52 (Jan.) 1939.

23a. Castiglioni, G., and Pepere, M.: Ricerche sperimentali intese a modificare il circolo splenico, Arch. ital. di anat. e istol. pat. **11**:14 (Dec.) 1939.

23b. Rousselot, L. M., and Thomson, W. P.: Experimental Production of Congestive Splenomegaly, Proc. Soc. Exper. Biol. & Med. **40**:705 (April) 1939.

A fact of the utmost importance for the proper understanding of this vascular condition was the observation that all these clinical and pathologic signs of congestion could also be found in the absence of any obstructive factor in the portal vessels. Such an event was rarely considered in its real significance, though it clearly resulted from the pathologic records of most of the instances of what was described as Banti's disease in the old and modern literature, and McNee [20b] had already noted that in Banti's disease high portal pressure and changes in the spleen precede the onset of marked fibrotic changes in the liver. Shortly thereafter Klemperer [12b] wrote that chronic portal stasis is not the sole cause of splenic enlargement and that cases have been observed in which the splenomegaly becomes clinically manifest at a period when there is no indication of a hepatic disorder. In other cases, he stated,[12b] the splenomegaly occurs concomitantly with the hepatic alterations and not subsequently; it is not dependent on or secondary to them. Six recent cases of congestive splenomegaly without peripheral obstacle to the venous return from the spleen were cited by me,[7] and 2 others have since come to my attention. Two similar instances were referred to by Larrabee.[4c] Twenty-two others have been collected by Rousselot,[6c] from a total of 55 cases of congestive splenomegaly under his observation in the spleen clinic of the Presbyterian Hospital of New York. If it were borne in mind that often the obstacle to the venous return from the spleen could not logically have accounted for the splenomegaly (frequently old splenomegalies are associated with slight cirrhosis or with recent thrombosis, as observed by Davies [24] and myself [7]), the number of cases of apparently nonsecondary splenomegaly would increase considerably.

Also the observations in cases of schistosomial splenomegaly are rather against the idea of ascribing the splenomegaly to the local deposition of ova and the subsequent fibrosis or to the thrombosis of large portal veins, which is extremely rare in this condition.[25]

MECHANISM OF SPLENIC CONGESTION

The absence of any obstruction in the portal bed is too frequent to be considered an insignificant exception; it forces one to the conclusion that an obstacle to the venous return from the spleen cannot be the first and common cause of the Banti syndrome in all cases and that the

24. Davies, J. C.: Splenic Anaemia and Portal Thrombosis, Lancet **2**:498 (Sept. 8) 1928.

25. Onsy, A. B.: The Pathogenesis of Endemic (Egyptian) Splenomegaly, Tr. Roy. Soc. Trop. Med. & Hyg. **30**:583 (April) 1937. Shafi, A. M.: Historical Review of Egyptian Splenomegaly and Allied Conditions, J. Egyptian M. A. **19**: 561 (Oct.); 631 (Nov.); 652 (Dec.) 1936.

opinion to the contrary, still held by the majority of authors,[26] should be discarded as contrasting with the pathologic evidence at present available.

A few hypotheses have been submitted to explain the congestion independently from an obstruction in the portal bed. Greppi and Cesaris Demel [27] stated the belief that the splenic engorgement was the consequence of the decreased contractility of the capsular and trabecular framework of the spleen. This was based on the opinion that the contraction of the intrinsic muscular framework of the spleen regulated the outflow of splenic blood. But muscle fibers are scarcely distributed in the human spleen, and the efficacy of their contraction is doubtful.[28] Also the rhythmic changes of splenic volume are caused not by a rhythmic contraction and relaxation of the smooth muscular framework of the spleen but by rhythmic variations in the blood flow.[29] By others [30] it has been suggested that the veins of the portal bed have a contractile, arterial-like function which actively helps the blood to overcome the peripheral resistance of the liver. Thus, it was suggested that the insufficiency of this function is the cause of the congestion. But, though portal vessels are rich in muscle fibers and endowed with high contractility, there is no evidence of their arterial-like activity. Nor could it be demonstrated that lesions of the walls of the portal vessels preceded the splenic congestion.

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26. Castle, W. B., and Minot, G. R.: Pathological Physiology and Clinical Description of the Anemias, New York, Oxford University Press, 1936, pp. 117-121. Magner, W.: A Textbook of Hematology, Philadelphia, P. Blakiston's Son & Co., 1938, p. 232. Rousselot.[6e]

27. Greppi, E.: Splenomegalie congestizie (da atonia): significato, patogenesi e cura, Boll. Soc. med.-chir., Catania **3**:446, 1935. Cesaris Demel, A.: Considerazioni sull'atonia dell'apparato muscolare contrattile della milza nella patogenesi di alcune splenomegalie, Baglivi **1**:200, 1935.

28. (*a*) Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 269. (*b*) Giunti, G.: L'apparato elastico-muscolare dello stroma splenico in diverse condizioni patologische (considerazioni sulla splenocontrazione e sulla splenoriduzione), Arch. ital. di anat. e istol. pat. **10**:123 (June) 1939.

29. Grindlay, J. H., and Herrick, J. F.: The Blood Resevoir Function and Rhythm of the Spleen: Preliminary Report of an Experimental Study, Proc. Staff Meet., Mayo Clin. **13**:663 (Oct. 19) 1938. Grindlay, J. H.; Herrick, J. F., and Mann, F. C.: Measurement of the Blood Flow of the Spleen, Am. J. Physiol. **127**:106 (Aug.) 1939. Grindlay, J. H.; Herrick, J. F., and Baldes, E. G.: Rhythmicity of the Spleen in Relation to Blood Flow, ibid. **127**:119 (Aug.) 1939. Bariéty, M., and Kohler, D.: Excitations urétérales et changements du volume de la rate chez les chiens normaux, yohimbinisés, atropinsés, cocaïnés et ésérinisés, Compt. rend. Soc. de biol. **127**:972, 1938.

30. Cellina, M.: Splenomegalie da alterato circolo portale e splenomegalie tromboflebitiche, Gior. di clin. med. **15**:615 (July 20) 1934. de Castro and dall'Acqua, G.: Osservazioni sulla splenomegalia tromboflebitica primitiva, Atti Soc. lomb. di chir. **3**:845, 1935.

To explain the genesis of splenic congestion, some other facts must be remembered: 1. The afflux of blood to the splenic pulp is regulated chiefly by the malpighian arteries and by other arteries in the pulp and in the trabeculae, which are rich in muscular tissue. It was noted by Knisely [31] that the contraction of the malpighian arteries is strong enough to obliterate their lumen. There are other vascular systems acting as capillary regulators which determine the afflux and the deflux of blood to and from the sinuses (Knisely [31]), but in the general economy of the splenic circulation, their importance is likely to be a local one, as their insufficiency could be counterbalanced by the muscular system of bigger arteries. 2. The output of splenic blood is limited by the peripheral resistance of the liver, which normally is small, being overcome by a portal pressure of 8 to 10 mm. of mercury. But when the splenic output increases above a definite amount, the blood can overcome the hepatic resistance only if the portal pressure rises adequately. 3. In instances of Banti splenomegalies, lesions of the malpighian and other small arteries—the most evident signs of which are periarteriolar hemorrhages and periarteriolar fibrosis—have constantly been found, even in early stages of the disease.

This last point gives enough evidence, I believe, to warrant the assumption that the small splenic arteries are the seat of early lesions. In consequence, their function of adjusting the intake of blood is altered, and blood enters the spleen in an increased quantity, which cannot be discharged through the hepatic resistance under normal conditions. Thus, the spleen becomes congested and widens; the elastic tension of the supporting framework increases, raising the pressure of the outflowing blood. This condition permits an increased amount of blood to pass through the small hepatic vessels.

The spleno hepatic circulation, altered in consequence of the insufficient regulating function of diseased splenic arterioles, is subject to a compensatory rise of venous pressure, which is a direct result of the splenic dilatation.

Becoming chronic, the splenic engorgement may be directly responsible for some lesions of the splenic pulp (fibrosis or hyperplasia), while the venous hypertension causes dilatation of splenic and portal veins and, eventually, their thrombosis. Further consequences are degenerative changes in the liver cells, which may not be extraneous to the genesis of portal cirrhosis.

Subsequently, either splenic thrombosis or cirrhosis of the liver, or both together, aggravate the portal congestion and may dominate the

31. Knisely, M. H.: Spleen Studies: I. Microscopic Observations of the Circulating System of Living Unstimulated Mammalian Spleens, Anat. Rec. **65**:23 (April 25) 1936; II. Microscopic Observations of the Circulating System of Living Traumatized Spleens and of Dying Spleens, ibid. **65**:131 (April 25) 1936.

further development of the disease. They are complications or associated morbid conditions and not the first cause of the congestion, because —as should always be remembered—splenic congestion may be found independent of either.

Obviously, the favorable effect of splenectomy or of ligation of the splenic artery (Greppi [10a] and Kemp [32]), which often, besides relieving the general and hematologic conditions, diminishes the tendency to gastroesophageal hemorrhages and ascites, is due to the removal of the primary cause of portal congestion. But some failure, often cited in the literature,[33] should have been foreseen, as splenectomy cannot remove the eventual thrombosis or the cirrhosis, nor can it always modify the state of gastroesophageal varices [34] or of the widespread dilatation of submucous and subserous small vessels of the esophagus and the stomach, which is frequently seen in cases of this kind (Ravenna [7] and Fiessinger, Albeaux-Fernet and Varay [35]).

COMMENT

It seems to me particularly significant that the present conception of primary splenic congestion is based on the undisputed presence of lesions in the small splenic arteries. Their fibrosis had been described by Banti [1]; the presence of regressive lesions in their walls and of endoarteritis had been noted by Gamna [13] and by myself.[7] The siderotic nodules themselves are the direct consequence of periarteriolar hemorrhages, as pointed out in 1902 by Marini,[36] the first author who described such lesions, and his interpretation was substantially confirmed by successive observers.[37] The significance of arteriolar lesions in the

32. Kemp, R.: Recurrent Haematemesis in Banti's Disease, Brit. M. J. **1**: 222 (Jan. 29) 1938.

33. Pemberton, J. deJ.: Results of Splenectomy in Splenic Anemia, Hemolytic Jaundice and Haemorrhagic Purpura, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1931, vol. 23, p. 539; Ann. Surg. **94**:755 (Oct.) 1931.

34. Hines, L. E., and Fitzgerald, B.: Splenomegaly of the Banti Type: Report of a Case with Postmortem Observations Four Years After Splenectomy, Arch. Path. **26**:155 (July) 1938. Kemp.[32] Greenwald, H. M., and Wasch, M. G.: The Roentgenologic Demonstration of Esophageal Varices as a Diagnostic Aid in Chronic Thrombosis of the Splenic Vein, J. Pediat. **14**:57 (Jan.) 1939.

35. Fiessinger, N.; Albeaux-Fernet, and Varay, A.: A propos des hémorrhagies persistantes après splénectomie, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:494 (March 18) 1938.

36. Marini, G.: Sopra un caso di splenomegalia con cirrosi epatica, Arch. per le sc. med. **26**:105, 1902.

37. Gandy, C.: Lésions particulières de la rate en un cas de cirrhose biliaire, Bull. et mém. Soc. anat. de Paris **80**:872, 1905. Eppinger.[3d] Gamna.[13] Christeller, E., and Puskeppelies, M.: Die periarteriellen Eisen- und Kalkinkrustationenx in der Milz, Virchows Arch. f. path. Anat. **250**:107, 1924. de Vecchi

mechanism of congestion, however, had never been considered before in human pathology, but recently Greppi [10] and Lenzi,[38] accepting the arguments discussed in my previous paper, admitted that the first lesion responsible for the splenic congestion might be an arteriolar one. Some experimental attempts to produce active congestion of the spleen were made by Henschen and Howald.[38a] They denervated the spleen of 3 dogs, in 2 of which splenomegaly was obtained. In view of their importance, these experiments should be repeated and enlarged, with the study of the alterations, if any, secondarily produced in the portal circulation and in the liver itself.

Episodes of Gastroesophageal Hemorrhages and Ascites.—Often this frequent and serious event in the course of the Banti syndrome puzzled the physicians by whom it had been attributed to an organic obstacle in the portal bed, which could not be found at the necropsy.[39] Hemorrhages and ascites may depend on the breakdown of the portal circulation, due to an anatomic obstacle (thrombophlebitis or cirrhosis), as well as to the progress of arteriolar lesions in the spleen and to a transitory increase of hepatic resistance, due to digestive or cardiac exigencies.

In many cases ascites appeared and disappeared quickly (Frugoni [3e]), and I think that this fact is rather against the idea of ascribing the condition to a definite anatomic obstacle, such as that represented by thrombosis or cirrhosis. The influence of digestive requirements on splenic circulation is great indeed, as it is proved by the increase of splenic volume during the normal digestive process, and therefore in splenomegalic patients the relation of the hematemeses to digestive phases should be investigated with greater attention.

Splenic Shrinkage After Administration of Epinephrine.—The shrinkage may depend on the stimulation of the splenic arterioles, the

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and Zanotti.[9b] Fasiani, G. M., and Oselladore, G.: Essai de réproduction expérimentale des nodules de Gandy-Gamna, Presse méd. **37**:1136 (Aug. 31) 1929. Jaeger, E.: Ueber Stauungsmilz, Verhandl. d. deutsch. path. Gesellsch. **26**:334, 1931; Milzbau und Kreislaufstörung, Virchows Arch. f. path. Anat. **299**:531 and 552, 1937. Alexandre, A., and Valducci, E.: Fattori che determinano le incrostazioni siderotiche della milza nei focolai sclerosiderotici, Pathologica **27**:321 (May 30) 1935.

38. Lenzi, F.: Sindrome Bantiana-splenomegalia fibroso-congestizia prevalentemente fibrosa-Contributo clinico-Ipotesi patogenetiche, Haematologica **22**:47, 1940.

38a. Henschen, C., and Howald, R.: Die anatomischen und klinisch-physiologischen Folgen der operativen Entnervung der Milz. Experimentelle Untersuchungen, Arch. f. klin. Chir. **157**:667, 1929.

39. Cellina.[2b] de Castro and dall'Acqua.[2b] Lucchi, G.: Morbo di Banti a lunghissimo decorso e splenomegalia tromboflebitica con trombosi della vena mesenterica superiore, Riv. di clin. med **35**:421 (July 15) 1934.

constriction of which decreases the intake of blood. Thus the shrinkage is due to the elastic retraction of the supporting framework. This conception, suggested by Colombi [40] and Villa,[20a] was adhered to by a detailed study of the musculature in the human spleen by Giunti.[28b] It is supported also by the evidence collected by Grindlay, Herrick and Baldes [29] in their experiments on the blood flow of the spleen. But it has not yet been noted that, if this mechanism be true, epinephrine should decrease the pressure in the splenic vein instead of increasing it. I do not know of any instance in which the pressure in the splenic vein was measured before and after injection of epinephrine, but the fact that the splenic shrinkage due to epinephrine never produced gastrointestinal hemorrhages, even when tried in patients who either previously or subsequently suffered from spontaneous gastrointestinal hemorrhages, speaks rather against the idea of ascribing the splenic reduction to an active contraction of the muscular framework. Obviously, an immediate episode of hemorrhage should have been a frequnet consequence if the epinephrine compressed the spleen and raised the portal pressure.

This mechanism also makes easy to understand why the splenic shrinkage may be of the same degree both when an obstructive factor is present and when it is lacking.[40a] If the epinephrine influenced the regimen of outflow, by actively expressing the blood from the spleen, a difference should have been noted under these two conditions.

A definite proof that in cases of splenic congestion epinephrine does not raise the portal pressure and a further indirect argument on its mechanism of action may be obtained by measuring the splenic venous pressure during surgical interventions. I hope that this will be tried in the near future.

As to the human spleen, the term "contraction" is, I believe, inadequate and probably incorrect; it may advantageously be substituted by "reduction" or "shrinkage," which merely describes the fact of the variation in size, without suggesting any determined mechanism.

Ascoli (Epinephrine) Therapy.—That the size of the spleen could be permanently reduced by intravenous injections of epinephrine was

40. Colombi, C.: La separata funzione del duplice substrato contrattile della milza, Atti Soc. lomb. di med. **2**:615, 1934.

40a. Greppi, E.: La negatività della splenocontrazione adrenalinica non esclude la natura sanguigna del tumore di milza, Policlinico (sez. prat.) **43**:53 (Jan. 13) 1936. Villa.[20a] Grenet, H., in discussion on Weill-Hallé, P.; de Gaudard d'Allaines, and Papaioannou, A.: Hématémèse et mélaena chez un enfant de neuf ans. Splénomégalie ancienne. Arrêt des hémorrhagies après splénectomie, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1481 (Dec. 6) 1937.

demonstrated by Ascoli, d'Alessandro, Riolo and Pizzillo,[41] who suggested injections of epinephrine hydrochloride as a new method of therapy for chronic malarial splenomegaly. Its favorable effect was confirmed by many authors.[42] The attempt to influence other splenomegalies with the same method is a logical consequence. The best results may be anticipated in cases of the Banti syndrome, in which the vascular factor plays such a great part.

I have tried this treatment on 3 patients, by injecting 0.01 mg. to 0.10 mg. of epinephrine hydrochloride intravenously on each of twenty successive days, as suggested by Ascoli and his associates. Two of these patients were suffering from a cryptogenetic Banti syndrome in an early stage. The spleen reached to about 3 inches (8 cm.) below the costal margin, and the liver was practically normal. A marked decrease of splenic size was obtained, without, however, influencing the general conditions. But the leukocytic count diminished quickly, in 1 case from 2,500 to 650 per cubic millimeter. Therefore, it was believed that further delay might be dangerous, and splenectomy was performed. The postoperative course was uneventful. Both patients were followed up for about a year, and they remained in good general and hematic condition. The third patient had an enormous splenomegaly and hypertrophic hepatic cirrhosis; years before he had suffered from malaria, and the serologic reactions proved that he was syphilitic. His poor condition contraindicated splenectomy. Antisyphilitic treatment together with Ascoli therapy caused permanent decrease of splenic size, a slight decrease of hepatic volume and satisfactory improvement of the general state.

Further experience is required, but I wish to suggest that it may be worth while to try Ascoli's method of treatment in cases in which surgical intervention on the spleen offers few chances of success. If the epinephrine lowers the portal pressure, this treatment might also decrease the danger of serious hematemesis in nonoperable patients.

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41. Ascoli, M.: Sulla cura dell'infezione malarica cronica, Riforma med. **52**: 351 (March 14) 1936. d'Alessandro, G.: Sulla cura di M. Ascoli della infezione malarica, Riv. di malariol. (sez. I) **16**:290, 1937. Riolo, P.: Sulla cura di M. Ascoli della infezione malarica, ibid. **16**:34, 1937. Pizzillo, G.: Sulla cura di M. Ascoli della infezione malarica, ibid. **17**:404 and 441, 1938.

42. Gosio, R.: Sondaggio di contrattilità della splenomegalia malarica e trattamento adrenalinico della stato malarico, Riv. di malariol. (sez. I) **16**:123, 1937. Mosna, E.: Sulla cura di M.Ascoli della infezione malarica, ibid. **17**:126, 1938. Nucciotti, L.: Ricerche sulla terapia adrenalinica nella malaria estivo-autunnale primitiva, ibid. **17**:131, 1938. Canova, F.: Associazione chinino-adrenalinica nel trattamento della malaria acuta, ibid. **16**:31, 1937. Froilano de Mello, J.: Experimental Studies on the Treatment of Malarial Splenomegalies by the Method of Ascoli, South African M. J. **12**:835 (Nov. 26) 1938.

SUMMARY AND CONCLUSIONS

Evidence has been accumulating which supports the view that Banti splenomegaly is largely due to splenic congestion and that this congestion is not dependent on an obstructive factor in the portal-venous bed. It is suggested that the congestion may be due to primary lesions of the small splenic arteries which regulate the blood flow into the spleen ("primary active congestion").

The human spleen should be considered as an elastic rather than as a contractile organ. Its variations in size depend on variations in volume of the inflowing blood, rather than on active contractions of the smooth muscle of its supporting framework.

From a mechanical point of view, the spleen might be defined as an automatic controller which regulates the pressure of the splenic venous blood in order to maintain the balance between the volume of inflowing blood and the amount which can be discharged through the hepatic resistance. Normally, and within certain limits, in pathologic conditions, the splenic elasticity guarantees a pressure sufficient to secure the further progress of venous portal blood. Congestive splenic enlargement is therefore a mechanism to counterbalance either increased volume of portal blood or increased peripheral resistance to the discharge of a normal amount of blood.

The Banti syndrome is a symptom complex dominated by chronic fibrocongestive splenomegaly, accompanied by portal hypertension and complicated by, or associated with, hepatic cirrhosis or thrombosis of the splenic and portal veins. It may depend on various causative agents, either infective or toxic. A scheme for its etiologic classification is presented.

The splenic changes of Banti syndrome are probably due to primary lesions of the splenic arterioles, the regulating power of which becomes insufficient to control the inflow of blood. The consequent congestive splenomegaly is the cause of the circulatory disturbance in the portal bed. Secondarily, hepatic cirrhosis and venous thrombosis may aggravate the state of portal circulation.

2900 Ellis Avenue.

Progress in Internal Medicine

GASTROENTEROLOGY

REVIEW OF LITERATURE FROM JULY 1939 TO JULY 1940

CHESTER M. JONES, M.D.
Physician, Massachusetts General Hospital; Clinical Professor of Medicine, Harvard Medical School
BOSTON

The widespread interest in gastroenterologic problems and their clinical importance is evidenced by the multiplicity of articles appearing in the world literature on all phases of the physiology of the alimentary tract, normal and abnormal, and the therapeutic applications directed thereto. Some new data have been added, particularly to the knowledge of the physiologic response of the digestive tract to various drugs, many of which are actively employed at present. In this review allusion will be made to strictly new discoveries and to new applications of old principles. It will also be my purpose, however, to call attention to many articles of clinical importance for the sake of reemphasizing recognized or partially recognized concepts of gastrointestinal disease.

PHYSIOLOGIC ASPECTS

Interest continues in the various factors influencing gastric secretion. In fact, attempts are still being made to obtain a satisfactory normal gastric secretory curve by varying technics. Wilhelmj and Sachs [1] still pursue their studies of gastric secretion following a test meal consisting of a specially prepared solution of Liebig's meat extract and a standard amount of phenolsulfonphthalein (phenol red). They believe that after such a test meal it is possible to determine what proportion of a given sample is fluid of the test meal remaining in the stomach and what proportion is due to secretions. The total secretions entering the stomach can be separated into acid and nonacid fractions, and the acidity of the total secretions can be determined independent of the acidity of the mixed gastric contents. Multiple curves on given subjects show a rather remarkable agreement, and the amount of acid secretion is usually constant in the same person. The increase in nonacid secretion due to regurgitation from the duodenum varies considerably even in the same

1. Wilhelmj, C. M., and Sachs, A.: The Characteristics of the Normal Human Gastric Secretory Curve Using an Improved Gastric Test Meal, Am. J. Digest. Dis. **6**:529, 1939.

person, with corresponding variation in the acidity of the total secretion entering the stomach. One interesing observation was made on the effects of mild acute alcoholism on the "morning after" in subjects on whom several curves had previously been obtained under normal conditions. There seemed to be a definite increase in the amount of acid secretion and a decrease in the amount of nonacid secretion, with a consequent elevation of the acidity of the total gastric contents. Values obtained among medical students appeared to be definitely higher than those noted previously in a group of free clinic patients. The authors suggest the possible importance of such a finding in relation to the higher incidence of duodenal ulcer in professional men and business executives. As a result of their studies Wilhelmj and Sachs [2] suggest that the final control of gastric acidity depends on at least two factors, namely, acid inhibition, which controls primarily the acidity of the gastric contents, and duodenal regurgitation, which controls primarily the acidity of the total secretions entering the stomach. Either mechanism may vary in different normal subjects and may fail in the presence of disease. They point out, however, that there still are several unknown factors, which make it difficult to establish any absolute figures for maximal and minimal secretory levels.

Among other factors influencing gastric secretion, that of advancing years has been recognized for some time. Bloomfield,[3] who has already called attention to the importance of this phenomenon, reports observations on 5 subjects who were reexamined after intervals of over ten years. Of the 5 subjects, 3 showed gastric secretion practically identical to that observed ten years previously; 1 showed a slight decline of acidity but not of volume of secretion, and 1 showed a diminution both in volume and in amount of acid. As Bloomfield points out, it is of real importance to carry out further and similar studies over long periods. He suggests the importance of associated gastroscopic observations to determine, if possible, whether any visible change in the mucosa occurs which can be correlated with alterations in gastric secretion. Why some normal persons preserve their gastric secretion unaltered over many years while others show a rapid decline in secretory activity is still entirely obscure. Bloomfield [4] also studied the effect of suggestion of a palatable food on gastric secretion. In these observations the food was not actually seen, smelled or tasted, but in 12 of 14 cases suggestion alone

2. Wilhelmj, C. M., and Sachs, A.: The Physiological Control of the Normal Human Gastric Secretory Curve, Am. J. Digest. Dis. **6**:467, 1939.

3. Bloomfield, A. L.: The Decrease of Gastric Secretion with Advancing Years: Further Observations, J. Clin. Investigation **19**:61, 1940.

4. Bloomfield, A. L.: Psychic Gastric Secretion in Man, Am. J. Digest. Dis. **7**:205, 1940.

was followed by an acceleration of secretion, the increase in volume being much more marked than the increase in acidity, in contrast to the stimulation normally observed after administration of histamine. The author explains this difference on the basis that psychic stimulation is transmitted to the stomach by way of the fibers of the vagus nerves, whereas histamine acts directly on the secretory cells. Such a conception is entirely comparable to the increase in motor activity to be noted under the fluoroscope when appetizing food is discussed.

The significance of gastric acidity after histamine stimulation was made the basis of a study by Ruffin and Dick [5] in a series of 2,877 gastric analyses. The writers made extensive studies of the acid values in this large group, of which 1,917 were normal persons, and concluded that there is a much wider range of variation in normal persons after administration of histamine than after use of the Ewald meal. They point out the fact, still not too generally accepted, that there is no such thing as a normal level of gastric acidity. The tremendous variation in acid values obtained by these and other investigators clearly illustrates the fallacy of the terms "hyperacidity" and "hypoacidity" except as implying relative levels of no real clinical significance. As in other studies, a significant difference in gastric acidity between men and women was observed. The mean for women was much lower than that noted for men. Confirmation of recent studies was obtained that there is no significant variation from the normal in patients suffering from rheumatoid or hypertrophic arthritis. The incidence of achlorhydria in this group of persons increases with age, as has now repeatedly been shown. The condition was frequently found in cases of cancer of the stomach and of pellagra, and it is of extreme interest that in 24 patients with active duodenal ulcers no free acid could be demonstrated after administration of histamine. The latter finding is highly suggestive in its implication that gastric hydrochloric acid at best is merely one important factor in the activity of peptic ulcer.

Katzenelbogen, Loucks and Gantt [6] performed experiments on dogs with Pavlov pouches in an attempt to condition gastric secretion to histamine. Their results were quite the reverse of those already alluded to as obtained by Bloomfield with human subjects. These authors found it impossible to elaborate a conditioned secretory reflex to histamine in their animals, and they explained such a failure as due to the fact that histamine acts peripherally. They compared, quite properly, the difference between the salivary secretion following the use of

5. Ruffin, J. M., and Dick, M.: The Significance of Gastric Acidity After Histamine Stimulation: A Statistical Study of 2,877 Gastric Analyses, Ann. Int. Med. **12**:1940, 1939.

6. Katzenelbogen, S.; Loucks, R. B., and Gantt, W. H.: An Attempt to Condition Gastric Secretion to Histamin, Am. J. Physiol. **128**:10, 1939.

pilocarpine hydrochloride, which is entirely due to peripheral stimulation, and that following the injection of morphine, which can be conditioned and which is known to have a definite central action.

An unusual action of histamine is suggested by the experiments of Ivy and Bachrach [7] as a possible explanation of the continuous secretion of gastric juice seen in some patients with ulcer and in patients with some other abnormal conditions. These authors noted that in 3 Mann-Williamson dogs with Pavlov pouches there was definite continuous hypersecretion, and in 1 animal there was definite hypersecretion in response to a meal. The gastric secretory mechanism reacted to atropine as though a portion of the secretory stimulus were histamine, the implication being that there had been an elaboration of histamine by an irritated or inflamed mucous membrane.

The favorable effect of pregnancy on the activity of ulcer has been noted by various investigators. Labate [8] reports studies on the effect of pregnancy on gastric secretion in 56 patients. For none of this group of pregnant women were the figures for gastric acidity above the so-called normal range, and for one fourth of the entire group the values were very low or complete achlorhydria was noted after administration of histamine. It is possible that the incidence of complete achlorhydria was no greater, however, than that to be anticipated in this particular age group. It is of interest that the average red blood cell count and hemoglobin concentration apparently showed a decrease as the gastric acidity diminished, although the author did not attempt to attribute the appearance of such anemia solely to alterations in gastric acidity. It is unfortunate that he did not complete his study by making similar examinations of the same group of subjects after delivery. Had such a study been made, the probable role of the endocrine factors operative during pregnancy might have been more clear.

Because of observations similar to those mentioned, such as those of Sandweiss and others, Culmer, Atkinson and Ivy [9] made studies on the effect on gastric secretion of the gonadotropic fraction of the urine of pregnant women. This substance was administered parenterally, and the gastric secretory response to a test meal was measured in 5 female dogs with Pavlov pouches. The authors chose the gonadotropic fraction of the urine of pregnant women for a study of the cause of the reduced acidity of gastric contents during pregnancy because this sub-

7. Ivy, A. C., and Bachrach, W. H.: An Abnormal Mechanism for the Excitation of Gastric Secretion in the Dog, Am. J. Digest. Dis. **7**:76, 1940.

8. Labate, J. S.: The Effect of Pregnancy on Gastric Secretion, Am. J. Obst. & Gynec. **38**:650, 1939.

9. Culmer, C. U.; Atkinson, A. J., and Ivy, A. C.: Depression of Gastric Secretion by the Anterior Pituitary-Like Fraction of Pregnancy Urine, Endocrinology **24**:631, 1939.

stance is produced in great quantities in women during the earlier period, when gastric secretion is reported to be most depressed, whereas in the dog it is not thought to be produced, and gastric secretion seems not to be depressed during pregnancy. After suitable control tests were made following injections of gonadotropic substance, significant to marked decreases in the volume of acid output occurred each day during a five day period of treatment. In 4 of 7 instances the secretory response returned to normal almost immediately. The activity of the gonadotropic substance was evidenced in that "estrus" occurred in 4 of 8 instances after its administration. The authors conclude that the gonadotropic fraction of the urine of pregnant women contains a substance which depresses the gastric secretory response of a dog to a meal, although they admit that the nature of the substance and its mechanism of action are still uncertain. Elsewhere Ivy [10] discusses the probability that the ulcer-preventing principle known to be present in urine is distinct from the gonadotropic substance in the urine of pregnant women. Extracts prepared from the urine of patients with peptic ulcer have been reported by Sandweiss to be lacking in the ulcer-preventing factor and by Freedman to contain the usual amounts of the principle that inhibits gastric secretion. Experiments are in progress at present to determine, if possible, the nature of the inhibiting factor found in urine ("urogastrone") and its identity, if this exists, with the inhibitory principle known to be present in duodenal extracts ("enterogastrone").

Further observations on the effect of insulin on gastric secretion are supplied by the studies of Horstmann,[11] who found on examination of 10 schizophrenic patients that in the presence of insulin coma a considerable rise in the acidity of the gastric secretion occurs after an initial fall. The rise begins after the level of blood sugar has reached its low phase, and the fall occurs after oral administration of cane sugar or dextrose and intravenous administration of dextrose in doses which terminate the effect of insulin. He also compared the effect of insulin with that of histamine as a stimulant to gastric secretion in 6 other patients, 5 of whom had achylia to alcohol test meals. Insulin proved to be more effective than histamine in causing a secretion of acid gastric juice and was said to produce acid gastric secretion when histamine had no effect.[12]

Numerous other studies on the stimulating or inhibiting effect of various substances on gastric secretion are reported. Shay and his

10. Ivy, A. C.: A Substance in the Urine Which Inhibits Gastric Secretion, editorial, Am. J. Digest. Dis. **7**:49, 1940.

11. Horstmann, P.: Investigation on Effect of Insulin on Gastric Secretion, Ugesk. f. læger **101**:935, 1939.

12. Horstmann, P.: Insulin Compared with Histamine as Stimulant of Gastric Secretion, Nord. med. (Hospitalstid.) **4**:3566, 1939.

collaborators,[13] for example, studied the effect on total gastric secretion of the instillation of neutral fat, fatty acids and soaps into the duodenum. A rather striking depression of all gastric secretory functions was noted, involving the production of acid, chloride and enzymes. The depression of secretion continued for a considerable period but usually was followed by a rise in all values. There appeared to be a difference between the motor and the secretory responses following such duodenal instillations and even between the secretion of acid and that of enzymes. Because the introduction of fatty substances into the duodenum prevented the expected stimulation of gastric secretion during insulin hypoglycemia, the authors conclude that this depression of gastric secretion represented chiefly an effect on the neurogenic phase of gastric activity. Such a conclusion, however, seems highly speculative, as they were unable by such measures to prevent a rise in gastric secretion following injection of histamine.

Pickett and Van Liere [14] noted in dogs with Pavlov or Heidenhain pouches that increasing degrees of anoxia caused proportional decreases in the volume of gastric secretion. Partial pressures of oxygen, corresponding to 8,000, 14,000, 18,000 and 24,000 feet, respectively, were employed. Gastric secretion in the animals with Heidenhain pouches was affected by much less severe degrees of anoxia than in the Pavlov group, a reduction in chloride being noted at an oxygen equivalent of 14,000 (94 mm. of mercury). This indicates that in part, at any rate, the reduction in gastric secretion associated with anoxia is due to vagal stimulation, and it is well known that anoxia is capable of stimulating the medullary centers.

Attempts to determine some correlation between the carbon dioxide content of the plasma and gastric acidity were made by Taylor and Michael.[15] Lowering of the plasma carbon dioxide to a level of 26 volumes per cent by the feeding of ammonium chloride caused no decrease in the free acid in Pavlov pouches in animals, although there was a great increase in the pouch secretion, which was attributed to a coincidental water intake due to the thirst produced by ingestion of ammonium chloride. Dehydration was effective in reducing the amount of pouch secretion but produced little or no change in gastric acidity.

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13. Shay, H.; Gershon-Cohen, J., and Fels, S. S.: The Role of the Upper Small Intestine in the Control of Gastric Secretion: The Effect of Neutral Fat, Fatty Acid and Soaps; the Phase of Gastric Secretion Influenced and Relative Importance of the Psychic and Chemical Phases, Ann. Int. Med. **13**:294, 1939.

14. Pickett, A. D., and Van Liere, E. J.: The Effect of Anoxia on Gastric Secretion from Pavlov and Heidenhain Pouch Dogs, Am. J. Physiol. **127**:637, 1939.

15. Taylor, F. W., and Michael, A. C.: Relation of Blood Carbon Dioxide and Dehydration to Gastric Acidity, Am. J. Digest. Dis. **7**:67, 1940.

Arieff [16] found that administration of sodium bromide to man caused displacement of the chloride ions in gastric secretion, as in the blood and other tissues, the chloride ion being displaced from 25 to 50 per cent. No significant changes in titratable acidity were noted, and there appeared to be no important retarding effect on peptic or tryptic digestion. Nutritional disturbances were noted only when there was anorexia or toxicosis.

Animal experiments on the effect of the barbiturates on gastric secretion were carried out by Coffey, Koppanyi and Linegar.[17] Using intravenous injections of sodium barbiturate and sodium amytal in large hypnotic and anesthetic doses, they noted a reduction in gastric secretion with a prompt return to normal after hypnotic doses and delayed return after anesthetic doses. The maximal postcibal excretion of the drugs in the gastric juice was approximately 5 per cent.

Exposure of the gastric mucosa to various solutions and its effect on the gastric response to histamine was studied by Mann and Mann.[18] Transitory achlorhydria was produced in dogs by introduction of a dilute solution of mercuric and cupric salts. Much greater concentrations of lead, manganese and zinc produced no effect. The use of quinone caused inhibition of gastric secretion, while hydroquinone and resorcinol had no effect in concentrations one hundred times as great. Brilliant green and crystal violet inhibited gastric secretion.

In addition to endocrine factors influencing gastric secretory activity, various observations have been made on the effect of specific diseases in this regard. That cholecystic disease tends to be associated with diminished gastric secretion of acid has been noted by various observers. The studies of von Murányi [19] on 64 patients with gallstones are of some interest, however, as gastric secretory curves taken after use of the Einhorn fraction test meal showed no uniform results prior to operation. Great individual differences were observed, and there was no evidence that gastric analyses were of diagnostic value in this condition. One fourth of the subjects had achylia or hypoacidity, but no significant discoveries were made in association with such complications as obstructive jaundice and acute cholecytitis. It is of interest that subsequent observations, made a year after cholecystectomy, revealed apparently normal

16. Arieff, A. J.: Effect of Sodium Bromide on Nutrition and Gastro-Intestinal Tract of Epileptic Patient, J. Lab. & Clin. Med. **25**:19, 1939.

17. Coffey, R. J.; Koppanyi, T., and Linegar, C. R.: The Effect of Barbiturates on Digestive Secretion, Am. J. Digest. Dis. **7**:21, 1940.

18. Mann, F. D., and Mann, F. C.: An Experimental Study of Some Chemical Inhibitors of Gastric Acidity, Am. J. Digest. Dis. **6**:322, 1939.

19. von Murányi, L.: Modifications in Secretions of Gastric Juice in Gallstone Diseases Before and After Extirpation of Gallbladder, Beitr. z. klin. Chir. **170**: 513, 1939.

values in nearly three fourths of the cases, whereas the original observations had revealed so-called normal values in only about 40 per cent.

Inconstant results in studies on the nature of the gastric secretion present in association with rheumatoid arthritis have been obtained since the original observations of Woodwark and MacKenzie, who apparently showed in 1912 that gastric achylia is a frequent associated finding. Studies reported by Edström [20] of 432 patients with this disease showed that nearly 20 per cent of the group had achylia refractory to histamine and that an additional 10 per cent had a very low level of gastric secretion. The achylia proved to be more frequent in cases of more severe involvement but was independent of the duration of the disease. Of 50 patients of this group subsequent examinations were made after long intervals, and it is of interest that only 12 of 23 patients with achylia at first refractory to histamine continued to show no gastric secretory response to stimulation with the drug. It must not be forgotten, however, that variations in the response to histamine also occur in normal subjects, as has been shown by Schiff, Palmer and others, the stomach at times being completely refractory and at other times entirely normal.

The relation between carcinoma of the stomach and the known reduction of gastric acidity has long been a matter for speculation. The observations of Brunschwig and Clarke [21] are of interest in this respect. Gastric analyses were made of a group of 70 patients with cancer of the stomach verified by operation or necropsy. Sixty per cent of the group exhibited achlorhydria, and an additional 15 per cent had hypochlorhydria. It is to be pointed out, however, that less than half of the patients were tested after the use of histamine, and it is probable, as the authors agreed, that the incidence of achlorhydria in the series would have been appreciably reduced had histamine been employed. A fairly accurate measure of the amount of carcinomatous tissue was obtained in each instance, and it was found impossible to demonstrate any definite relation between the size of the tumor and achlorhydria. Actually, the surface area of the cancer in patients with achlorhydria averaged much less than half of that noted in patients with normal types of secretion. Neither was there any evidence to indicate a definite relation between the histologic type of the cancer and the quality of gastric secretion, although in this small group there seemed to be a suggestion that the scirrhous type of carcinoma was accompanied by achlorhydria less frequently than were the other types.

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20. Edström, G.: Gastric Secretion and Basal Metabolism in Chronic Rheumatic Arthrides, Acta med. Scandinav. **99**:228, 1939.

21. Brunschwig, A., and Clarke, T. H.: Histologic Structure of Carcinomas of the Stomach and Quality of Gastric Secretions, Ann. Int. Med. **13**:1001, 1939.

Brunschwig and his associates [22] have amplified work previously reported on the depressant effect of gastric juice obtained from patients with pernicious anemia. Intravenous injection of gastric juice from 18 patients with pernicious anemia resulted in a marked transitory depression of pouch secretion in dogs and in achlorhydria in 90 per cent of samples taken, as contrasted with the results obtained by injection of gastric juice obtained from 34 hospital patients without pernicious anemia or malignant disease. With the latter, gastric secretory inhibition was noted in less than one fifth of the observations. These investigators also showed [23] that samples of achlorhydric gastric juice taken from patients with cancer of the stomach produced a similar inhibition of gastric secretion in nearly 80 per cent of the experiments. The significance of such findings is far from clear as gastric inhibition was noted after use of material from patients not suffering from pernicious anemia or cancer, although previous control experiments had indicated that gastric juice from apparently normal persons has no inhibitory effect.

Attempts to correlate vitamin C deficiency and achlorhydria fail to show any correlation. Nordström [24] was unable to demonstrate any reduction of the acidity of gastric juice following injection of histamine after production of an absolute deficiency vitamin C in guinea pigs. Herrin [25] was unable to demonstrate any change from normal in the free and total acids in the gastric juice and the rate of secretion in response to histamine in dogs on a diet absolutely deficient in vitamin A. Subsequent administration of vitamin A to these animals produced no significant changes.

Some further light on the mechanism of secretion of hydrochloric acid in the stomach is afforded by the studies of Davenport.[26] This investigator demonstrated in cats, rats and dogs that carbonic anhydrase is present in the parietal cells of the gastric mucosa but not to any appreciable extent in the surface epithelium of the gastric mucosa, in the chief cells or in the fundic cells. A small amount appears to be present in an unidentified cell in the pyloric antrum of the rat. In cats and rats

22. Brunschwig, A.; Van Prohaska, J.; Clarke, T. H., and Kandel, E. V.: A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia, J. Clin. Investigation **18**:415, 1939.

23. Brunschwig, A.; Clarke, T. H.; Van Prohaska, J., and Schmitz, R. L.: A Secretory Depressant in the Achlorhydric Gastric Juice of Patients with Carcinoma of the Stomach, Surg., Gynec. & Obst. **70**:25, 1940.

24. Nordström, T.: Experimental Investigations of the Hydrochloric Acid Secretion in Scorbutic Guinea-Pigs, Acta med. Scandinav. **99**:443, 1939.

25. Herrin, R. C.: Gastric Emptying Time and Acidity in Avitaminosis in Dogs, Am. J. Digest. Dis. **7**:164 1940.

26. Davenport, H. W.: Gastric Carbonic Anhydrase, J. Physiol. **97**:32, 1939; Gastric Carbonic Anhydrase in Dogs, Am. J. Physiol. **128**:725, 1940.

the concentration of this substance in the parietal cells is several times greater than that noted in the red blood corpuscles. The fact that there is a high concentration of carbonic anhydrase in the parietal cells leads to the supposition that carbonic acid may play an important role in the mechanism of formation of hydrochloric acid. This author [27] found that sodium thiocyanate inhibits the ability of carbonic anhydrase to catalyze the hydration and dehydration of carbon dioxide and inhibits secretion of acid by the gastric mucosa of dogs. He explains this inhibition of secretion by the assumption that sodium thiocyanate inhibits the carbonic anhydrase, which is a part of the secretory mechanism, and apparently shows that the rate of secretion of acid by the gastric mucosa is directly proportional to the rate of formation of carbonic acid in the secretory mechanism.

To those interested in animal experimentation, the new type of gastric pouch described by Cope and his collaborators[28] will be of interest. These authors confirm the previous observations that the vagal supply of the Pavlov type of gastric pouch is not intact. They describe a gastric pouch in the dog, made from the anterior wall of the body of the stomach, which has the advantage of an intact autonomic nerve supply, both vagal and sympathetic, with only partial denervation of the residual portion of the stomach distal to the collecting pouch. The mechanical stimulation of secretion is reduced to a minimum by obviating the necessity of an inlying cannula, and care of the animal is greatly facilitated.

In a further study on the physiologic effects of gastric mucin, Wigodsky, Bussabarger and Fogelson [29] noted the effects of gastric mucin on regeneration of hemoglobin in anemic dogs. Commercial preparations of gastric mucin appeared to stimulate the production of hemoglobin in anemic dogs from 55 to 70 per cent more than could be accounted for by the amount of iron present in the preparation. However, the stimulus was not so great as that noted when beef liver was fed.

Within the past ten years experiments have been carried out on animals in an attempt to find a reliable method of detecting the presence of antianemic substances. Singer, in 1935, found that injection of normal gastric juice into old albino rats caused a characteristic increase in the number of circulating reticulocytes and concluded that the presence or

27. Davenport, H. W.: The Inhibition of Carbonic Anhydrase and of Gastric Acid Secretion by Thiocyanate, Am. J. Physiol. **129**:505, 1940.

28. Cope, O.; MacMahon, C. E.; Hagströmer, A., and Thompson, R. H.: Gastric Secretion: I. A New Gastric Pouch with a Nonleaking Stoma and an Intact Nerve Supply; Description of a Two-Stage Technic Used on the Dog, Arch. Surg. **40**:717 (April) 1940.

29. Wigodsky, H. S.; Bussabarger, R. A., and Fogelson, S. J.: The Effect of Gastric Mucin on the Hemoglobin Regeneration in Anemic Dogs, J. Lab. & Clin. Med. **25**:13, 1939.

absence of the "intrinsic hematopoietic factor" in any given specimen of gastric juice could be determined readily. By similar studies, Schlicke [30] was unable to confirm these conclusions. Neither oral nor intramuscular injections of gastric juice and gastric juice concentrates produced any consistent or predictable changes in the number of circulating reticulocytes in rats. He concluded that the variable reticulocyte response to gastric secretion, which is nonspecific, is unreliable in detecting the presence of antianemic substances.

Various studies have been made on alterations in the motor activity of the stomach. Gordon and Singleton [31] made observations on dogs and describe in detail two types of gastric peristalsis, the first involving all coats of the stomach, purely propulsive and with wide swings, and the second involving only the mucosa and the muscularis mucosae, its function apparently being propulsive and also having an added mixing effect on the gastric contents. As this second type of peristaltic wave passes distally, tonic changes occur in the muscularis propria.

Van Liere and Sleeth [32] present an interesting review of the literature on the effects of acid and of alkali on gastric motor activity. To a series of healthy medical students known to have hydrochloric acid in their fasting gastric juice, a standard test meal was given, to which had been added a standard amount of barium sulfate. The normal emptying time was ascertained by repeated fluoroscopic examinations. There was considerable individual variation, but in any given subject motor activity appeared to be constant under the experimental conditions. It was found that therapeutic doses of hydrochloric acid produced a slight but not very significant delay in the emptying time for such subjects. On the other hand, a therapeutic dose of sodium bicarbonate (5 Gm. in 100 cc. of water) was followed by an average increase of over 16 per cent in the emptying time of the stomach. In order to determine whether the result was due to alkali or to carbon dioxide, a therapeutic dose of disodium phosphate was used, and this produced an almost identical increase in the rapidity of gastric emptying. Such a study presents more or less quantitative evidence as to the effects of therapeutic doses of commonly used acids and alkalis on the motor response of a normal stomach, but the actual mechanism involved is still not clear. The authors suggest three possible mechanisms: (1) a direct effect on the pylorus; (2) stimulation of motor activity associated

30. Schlicke, C. P.: Studies on the Effect of Human Gastric Juice in the Reticulocytes of Albino Rats, Am. J. Digest. Dis. **7**:277, 1940.

31. Gordon, S., and Singleton, A. C.: Gastric Peristalsis, Surgery **6**:697, 1939.

32. Van Liere, E. J., and Sleeth, C. K.: The Emptying Time of the Normal Human Stomach as Influenced by Acid and Alkali with a Review of the Literature, Am. J. Digest. Dis. **7**:118, 1940.

with stimulation of the gastric secretion by the alkali, and (3) a direct effect on the gastric musculature. None of these theoretic explanations is entirely satisfactory.

Using a somewhat similar method, Reynolds and his associates[33] studied the gastrointestinal response of children to test meals consisting of various types of milk to which had been added barium sulfate. The 7 healthy children included in this study had been observed previously in an acid-base, mineral balance study covering more than seven months, and all gastrointestinal motility patterns were already known. Roentgen examinations were made frequently over a period of seventy-two hours. The soft curd milks (evaporated and base exchanged) left the stomach in much less time than did pasteurized milk and appeared to have a more orderly progression throughout the entire alimentary canal. Subsequent studies were made,[34] comparing the rate of emptying in water, milk, cream, meat and carbohydrate mediums. In this study over 300 exposures illustrated variations among individual responses to the same meal and different meals and in the response of different sections of the alimentary canal. The water meal produced the most consistent and constant reactions in both the stomach and the intestine, and the milk, cream and carbohydrate meals were all subject to an initial delay in gastric emptying, the greatest retardation following the intake of cream. The meat meals, containing 7 per cent protein and 3.5 per cent fat, produced less delay in gastric emptying than that caused by cream and made more rapid progress through the small intestine until the terminal portion of the ileum was reached. At this point the protein-fat mixtures seemed to exert a stronger motor inhibition than did the cream mediums. After the initial delay in gastric emptying, the carbohydrate meal filled the entire small intestine very rapidly, and at the same time the stomach increased in size, indicating the extreme rapidity of action of a mechanism tending to bring the contents of the stomach to isotonicity by osmotic induction of water into it. None of these data are surprising or distinctly new, but they offer an interesting confirmation of views previously held.

The effect of products of protein hydrolysis in inhibiting gastric motility was studied by Thomas and Crider.[35] These authors introduced

33. Reynolds, L.; Macy, I. G., and Souders, H. J.: The Gastrointestinal Response of Children to Test Meals of Barium and Pasteurized, Evaporated, and Base-Exchanged Milks, J. Pediat. **15**:1, 1939.

34. Reynolds, L.; Macy, I. G.; Hunscher, H., and Olson, M. B.: The Gastro-Intestinal Response of Average, Healthy Children to Test Meals of Barium in Milk, Cream, Meat and Carbohydrate Media, Am. J. Roentgenol. **43**:517, 1940.

35. Thomas, J. E., and Crider, J. O.: Inhibition of Gastric Motility Associated with the Presence of Products of Protein Hydrolysis in the Upper Small Intestine, Am. J. Physiol. **126**:28, 1939.

numerous materials resulting from commercial or in vivo hydrolysis of proteins into the small bowel. All of the substances except the amino acid mixtures caused inhibition of gastric motility within fifteen seconds, in a manner comparable to the effect of hydrochloric acid. Bilateral vagotomy prevented the occurrence of such an inhibition on gastric motility, and the authors conclude that the products of protein hydrolysis produce inhibition of gastric motility by acting in the intestine as stimuli for the enterogastric reflex.

Herrin [25] studied the gastric emptying time of dogs under conditions of vitamin A deficiency. For one half of the animals the final gastric emptying time was increased appreciably, but in the remainder of the group of experimental animals there was no significant deviation from the normal. The variability of the results as regards the effect of avitaminosis A on gastric emptying time was thought to be due to changes in the central nervous system rather than in the alimentary tract.

Further evidence of the influence of hypothalamic stimulation on gastric motility is presented by Wang and his associates.[36] They made direct observations on more than 50 animals (cats) by a faradic stimulation with light anesthesia of the hypothalamic area. The effects of such stimulation on the gastrointestinal tract were visualized by means of a transparent window or recorded by the balloon method. Stimulation of the hypothalamus anterior to the infundibular region caused immediate blanching and occasional inhibition followed by a marked excitatory response. The onset of the latter was slow and gradual, and its effect lasted for several minutes. Section of both vagus nerves did not abolish this effect. Vagal effects were obtained when the hypothalamus at or behind the infundibular level was stimulated. Such a response could be elicited in chronic spinal cats and was abolished after bilateral vagotomy.

Further studies on the absorption of dextrose solutions by the stomach were made by Shay and his collaborators.[37] Contrary to most previous studies but in accordance with some other recent ones, these authors found that considerable amounts of dextrose may be absorbed by the stomach alone when the solutions are of high concentration. From dextrose concentrations below 15 per cent no appreciable absorption could be demonstrated. Studies on absorption and dilution by the

36. Wang, S. C.; Clark, G.; Dey, F. L., and Ranson, S. W.: Further Study on the Gastro-Intestinal Motility Following Stimulation of the Hypothalamus, Am. J. Physiol. **130**:81, 1940.

37. Shay, H.; Gershon-Cohen, J.; Fels, S. S., and Munro, F. L.: The Absorption and Dilution of Glucose Solutions in the Human Stomach and Duodenum, Am. J. Digest. Dis. **6**:535, 1939.

duodenum as contrasted with the stomach were made possible by the use of a multilumen tube. It was demonstrated that as a diluting organ the importance of the stomach is much less than that of the duodenum, the latter showing remarkable powers in changing from an organ of dextrose absorption to one of dextrose dilution. The best absorption of dextrose from the duodenum was usually noted in solutions at or near isotonicity. With hypertonic solutions the duodenum is capable of mobilizing enormous quantities of fluid in short periods, and the greater the concentration above isotonicity, the greater will be the dilution and correspondingly, the less the actual absorption. There appears to be a reciprocal shift of chloride to dextrose concentration in the duodenum in the attempt to maintain isotonicity. It is of incidental interest that Shay and his co-workers [38] carried out studies also on the absorption of hydrochloric acid in the human stomach. They were unable to demonstrate any absorption, even from solutions in a concentration of 1 per cent. With this concentration gastric secretion was obviously completely inhibited.

Cannulation of gastric and duodenal fistulas in dogs provided the basis for observations on estimations of gastric and duodenal p_H experiments carried out by Thomas.[39] It was found that under conditions designed to produce the maximal normal acidity in the intestinal contents during digestion the acidity in the duodenum near the pylorus rarely exceeded a p_H of 3 and was generally near a p_H of 4. The acidity was less in other parts of the duodenum and in the upper part of the jejunum. The contents of the pyloric antrum near the pylorus, as could have been predicted, were consistently less acid than the contents of the body of the stomach, a reaction usually between a p_H of 2 and 3. The authors suggest that the "receptive relaxation" of the duodenum, by causing accumulation of the duodenal contents in the vicinity of the pylorus at the moment of exit of gastric contents, facilitates quick dilution and partial neutralization of the chyme. It is obvious, however, that dilution can be quickly accomplished by the rapid outpouring of fluid in the presence of hypertonic solutions, as has already been noted by Shay and others.

An unusual finding is that reported by Herrin [40] on the secretion of ammonia in the succus entericus obtained from a Thiry-Vella loop of jejunum in the dog. The concentration of ammonia in the juice was

38. Shay, H.; Gershon-Cohen, J., and Fels, S. S.: The Absorption of Hydrochloric Acid by the Human Stomach, Am. J. Digest. Dis. **6**:361, 1939.

39. Thomas, J. E.: The Maximal Acidity of the Intestinal Contents During Digestion, Am. J. Digest. Dis. **7**:195, 1940.

40. Herrin, R. C.: The Secretion of Ammonia by the Small Intestine of the Dog, Am. J. Physiol. **129**:146, 1940.

influenced by a number of factors. It could be increased by giving a high protein diet and diminished by changing to a diet high in carbohydrate. The ammonia content of the jejunal secretion paralleled changes in the urinary excretion of nitrogen. Intravenous injection of certain amino acids resulted in a marked increase in the ammonia content of the juice, as did injection of insulin. The author interpreted his observations by assuming that the ammonia was secreted by the glands of the jejunum. Its concentration in the juice appeared to be determined largely by the protein metabolism of the gland cells; it apparently served no physiologic purpose as far as digestion was concerned, and it appeared in the juice and the blood from the intestine because of its easy diffusibility.

New and ingenious methods of study have permitted renewed investigations of the mechanism of the motor activity of the gastrointestinal tract that are worthy of notice. Weltz,[41] by the use of planekymograms, has made a series of fluoroscopic observations on the motor activity of the entire gastrointestinal tract. What he interprets as evidence of tonus in the stomach is apparently the factor controlling peristalsis. With a low degree of tonus, peristalsis frequently becomes quiescent; with the increase of tonus, peristalsis starts suddenly; but if tonus again decreases, peristalsis may cease. The starting of gastric peristalsis after filling of the stomach may be the result of the stretching stimulus, but this of necessity must diminish with progressive emptying of the organ, and peristaltic emptying of the last traces of gastric contents cannot be explained by the stimulus of distention. The complete emptying of the stomach can be understood only by assuming a steady increase in tonicity during the act. In the presence of pyloric stenosis due to carcinoma, irregular cufflike contractions and spasm of the antrum may occur instead of nomal peristalsis, and they are similar in appearance to the contractions noted in the first stage of vomiting. In the small bowel the author noted peristaltic waves and, in addition, a second kind of propulsive movement, which occurred especially if large quantities of gastric contents were suddenly emptied into the intestine. A similar picture is noted in the presence of pyloric insufficiency and in the stomach after an operation. The usual picture of colonic movement is one of slight restlessness of the haustra, with frequent increases in haustral activity in a single segment. Stomach-like peristalsis was observed in the middle of the transverse colon in the presence of partial obstruction. Complete obstruction of the colon was associated with repeated cufflike contractions similar to those noted in the region of the pylorus in the presence of obstruction.

41. Weltz, G. A.: Motility of the Gastro-Intestinal Tract in Man as Observed in Planekymograms, Radiology **33**:462, 1939.

An entirely different approach was that made by Bozler,[42] who carried out electrophysiologic studies on the action potentials of the stomach and small intestine in animals. Muscle contractions were accompanied by a repetitive discharge and were, therefore, analogous to a tetanic contraction of skeletal muscle. The frequency of discharge ranged from about 1 per second during gastric peristalsis to 10 per second during a peristaltic rush in the small intestine. Grading of the contractions was made possible by noting the variation in the number and frequency of impulses. The size of the impulses varied with the strength of the contractions, probably because only part of the musculature was active during weak contractions. The peristalsis in the small intestine of the cat and dog appeared to consist of rhythmic contractions on the oral side of a bolus, whereas the peristaltic rush in the rabbit was a continuous wave of contraction.

Douglas and Mann,[43] using exteriorized loops of small intestine at different levels, noted the occurrence and rate of rhythmic contractions in dogs. Rhythmic contractions were found to be a relatively rare form of movement in these preparations, but their rate was practically a constant for any given loop. The rate for any given loop was found to be a function of its distance from the pylorus, the loop at the highest level having the highest rate and that at the lowest level a correspondingly lower one. The rate was not affected by fasting, feeding or sleep, except that in recently fed animals rhythmic contractions were less commonly observed than in fasting animals. Degenerative vagal and splanchnic section did not affect the rate of these contractions. These investigators also studied the activity of exteriorized loops of the lower part of the ileum in continuity in relation to the ingestion of food. A regular cycle of activity was noted in the normal animal, namely, a rapid motor response to feeding followed by prolonged activity which gradually diminished until, after forty-eight hours of fasting, the activity was extremely feeble. The motor response was noted as constant after feeding by gastric fistula, as in the normal animal, and was not affected by double vagotomy at the level of the thorax. Partial interruption of continuity by a short-circuiting operation caused inconstant results, but complete isolation of the loop resulted in absence of the motor response to feeding and complete dissociation of the activity of the loop from ingestion of food. The authors take this evidence to indicate that the degree and type of activity at the lower portion of the ileum in the dog

42. Bozler, E.: Electrophysiological Studies on the Motility of the Gastro-Intestinal Tract, Am. J. Physiol. **127**:301, 1939.

43. Douglas, D. M., and Mann, F. C.: An Experimental Study of the Rhythmic Contractions in the Small Intestine of the Dog, Am. J. Digest. Dis. **6**:318, 1939; The Activity of the Lower Part of the Ileum of the Dog in Relation to the Ingestion of Food, ibid. **6**:434, 1939.

is intimately connected with the ingestion of food; that the so-called gastroileac reflex is not merely a feeding reflex but depends for its mediation on the continuity of the intestine, and, finally, that the vagus nerves, which are generally believed to be the motor nerves of the small bowel, play little part in its mediation.

More complete experiments were carried out,[44] in which loops of jejunum, ileum and colon were exteriorized in continuity, and further studies were made on the so-called gastroileac reflex in relation to feeding. A prompt motor response following feeding was noted in both the jejunal and the ileac loops, occurring more rapidly in the jejunal loops than in the ileac. Moreover, in an animal in which two exteriorized loops of small intestine at different levels were prepared, the motor response constantly appeared in the loop at the higher level before appearing in the lower loop, a finding entirely in keeping with the observations of Bozler, to which reference has already been made, and with previous studies, including those of Alvarez on intestinal gradients. Feeding by duodenal fistula gave as constant results as oral feeding, and section of the intestine orad to the loop and reanastomosed in such a way as to prevent union of the muscular coats and the intrinsic enteric plexuses did not prevent occurrence of the motor response. A constant motor response after feeding was noted in the distal part of the colon but not in the proximal part. These findings suggest that after ingestion of food a wave of activity traveling at the rate of about 1 cm. per second passes down the length of the small intestine. The gastrocolic reflex does not appear to be a part of this excitation, and the authors suggested that the term "gastroileac reflex" is not sufficiently inclusive.

By means of cinematography, Barclay [45] observed the movements of the terminal portion of the ileum and the action of the ileocecal "valve." Activity in this region was stimulated by the intake of food. Two main types of contraction were noted—a propulsive or rapid rush movement, and a churning, slow nonpropulsive movement. In the records obtained the ileocecal "valve" did not appear to act in a valvular manner to prevent the passage of food. Although capable of contraction, it was seen in some of the records to be wide open and empty and in others to be wide open and full, with no sign of narrowing. There was no indication that ileal contents were pressed up against it as at the pylorus. The author gained the impression that normally at this region it exerts little influence on the passage of food. He believes, however, that in the presence of local inflammatory condi-

44. Douglas, D. M., and Mann, F. C.: The Gastro-Ileac Reflex: Further Experimental Observations, Am. J. Digest. Dis. **7**:53, 1940.

45. Barclay, A. E.: Intestinal Movements in the Ileocecal Region, Radiology **33**:170, 1939.

tions it may exert a valvular action, as indicated by the delay noted in this region in disease of the appendix.

Bargen, Wesson and Jackman [46] contributed an embryologic review and anatomic study of the musculature, blood and lymphatic supply of the ileocecal junction of man. They believe it has been demonstrated in man that the circular and longitudinal muscles of both the ileum and the colon enter the labia of the ileocecal junction and comprise a structure with sphincteric action. Observations in 2 patients on the results of stimulation of this region, with resulting contraction and relaxation, suggest to the authors that its function is concerned with the production of a barrier between the ileum and the colon when such a barrier is needed. They also suggest that the demonstration of a lymphatic block at the tip of the labia of the ileococecal junction is of some clinical interest, as it may help to explain the limitation of cancerous growths of the ileocecal junction to the cecal side as well as the fact that melanosis coli does not advance proximally beyond this region.

Kleitsch and Puestow [47] noted the effect of intravenous solutions commonly used in surgical practice and of insulin on the peristaltic rate and tonus in isolated intestinal transplants. Physiologic sodium chloride solution administered by drip venoclysis produced a definite increase in the rate and strength of the contractions, whereas 10 per cent dextrose solution had little, if any, effect on motility of the small bowel. Insulin caused a progressive diminution in peristaltic rate and strength and in intestinal tonus when administered alone or combined with a solution of dextrose.

Brandberg [48] presents an interesting experimental study on intestinal motility in mechanical ileus. Observations were made on rabbits in which obstruction by obturation or strangulation was established at different levels in the intestinal tract. The results were studied by the abdominal window method and confirmed the view that in mechanical ileus there first sets in a stage of increased motility in the intestine above the obstruction, followed by a stage of paralysis due undoubtedly to distention of the bowel and impaired circulation of the blood. The stage of increased motility varies greatly in duration with the situation of the obstruction. With obstruction of the upper part of the small intestine this stage is short, and distention and paresis rapidly set in. The lower the obstruction is situated, the more favorable are the con-

46. Bargen, J. A.; Wesson, H. R., and Jackman, R. J.: Studies on the Ileocecal Junction (Ileocecus), Surg., Gynec. & Obst. **71**:33, 1940.

47. Kleitsch, W. P., and Puestow, C. B.: Studies of Intestinal Motility: The Effect of Intravenous Solutions and of Insulin upon Peristalsis, Surgery **6**:679, 1939.

48. Brandberg, R.: An Experimental Study of Intestinal Motility in Mechanical Ileus, Acta chir. Scandinav. **83**:287, 1939.

ditions, and in consequence a long period of increased bowel movements occurs, especially in cases of obstruction of the distal portion of the colon, paresis setting in only gradually and then not completely. The earlier view that in cases of obstruction by strangulation the motility in the parts of the intestine above the obstruction is initially less lively than in cases of obstruction by obturation did not prove to be correct. Although these results are not surprising, the fact that they offer accurate visualization and confirmation of clinical impressions makes them of practical value.

Absorption of various material from the small bowel continues to offer an excellent opportunity for investigative work and has a practical bearing on various therapeutic problems. One study of real interest is that reported by Dennis and Visscher [49] on the influence of various factors on intestinal absorption involving osmotic work in the dog. Active absorption against large concentration gradients occurs from the lower part of the ileum of the trained unanesthetized dog. Thiry-Vella loops from the upper, middle and lower portions of the ileum, in the order named, show progessively more rapid absorption. Of especial interest is the fact that true excitement was found to be associated with a diminished absorption rate. Anesthetization of excitable dogs increased the rate of active absorption, whereas anesthetization of placid dogs caused no such change. Excitement caused blanching of the ileal mucosa, suggesting the observations previously alluded to on blanching of the bowel following hypothalmic stimulation. The rate of active absorption is faster in chronic loop experiments than in acute experiments. Ingestion of food does not alter absorption rates outside the limitis of normal variability.

Van Liere and Vaughan [50] report experiments confirming the statement that chloride ion is absorbed from the intestine against a diffusion gradient in the presence of a polyvalent anion (sulfate). This absorption of chloride against a diffusion gradient is reduced but not prevented by anoxia, which, however, has no effect on the absorption of sodium chloride from the mammalian small intestine.

An interesting abnormality of intestinal absorption is that studied by Dennis and Wood [51] in adrenalectomized dogs. The animals were maintained on high sodium, high bicarbonate, low potassium diets after

49. Dennis, C., and Visscher, M. B.: The Influence of Various Factors upon Intestinal Absorption Involving Osmotic Work in the Unanesthetized Dog, Am. J. Physiol. **129**:176, 1940.

50. Van Liere, E. J., and Vaughan, P. E.: The Influence of Anoxia on the Absorption of Sodium Chloride and Sodium Sulphate from the Small Intestine, Am. J. Physiol. **129**:618, 1940.

51. Dennis, C., and Wood, E. H.: Intestinal Absorption in the Adrenalectomized Dog, Am. J. Physiol. **129**:182, 1940.

the withdrawal of the adrenal cortical hormone. In such a condition, there was a marked decrease in the rate of absorption of sodium, potassium and chloride from the ileum, a situation that was reversed in every case by the administration of an extract of adrenal cortex. When the cortical extract was withdrawn, the rate of sodium absorption in general declined more than that of potassium absorption, and at times there seemed to be an actual reversal in the direction of sodium, which was sometimes excreted into the intestine in relatively large quantities, although potassium was still being absorbed. In spite of essentially normal blood chemistry and objectively excellent health, the behavior of the intestine in the adrenalectomized dog could not be maintained in the absence of adrenal cortical hormone.

The effect of another endocrine secretion on intestinal function was studied by Althausen, Kerr and Stockholm,[52] who report further experiments on the calcium exchange of the intestine in the presence of experimental hyperthyroidism. They showed that administration of thyroxin, of subpurgative doses of castor oil or of cascara practically doubled the fecal output of calcium in rats. Restriction of the food intake or administration of morphine markedly decreased the excretion of calcium in hyperthyroid rats. The authors, therefore, conclude that hyperperistalsis and overeating are the chief causes of increased fecal output of calcium in hyperthyroid rats maintained on a calcium-free diet. They noted no appreciable change in calcium absorption in the presence of hyperthyroidism.

Absorption of iron from the gastrointestinal tract was studied by Moore and his collaborators.[53] Owing to the fact that serum iron has been demonstrated to be transport iron, a new approach to the study of absorption of iron from the gastrointestinal tract was available, although the measure of serum iron reflected the fact and degree of absorption rather than the total amount. From the data available in the literature and those acquired in this investigation, the following picture of iron absorption was constructed: When ingested iron reaches the stomach, it is subjected to the influences of the prevailing acidity, the free gastric hydrochloric acid apparently having two functions; first, to ionize and dissolve iron not already present in solution or not in an ionized state and, second, to delay the formation of insoluble and undissociated iron compounds. Since these form at a p_H above 5, some change would appear to occur in the stomach of patients with achlorhydria. Iron delivered into the duodenum is subjected to two influences,

52. Althausen, T. L.; Kerr, W. J., and Stockholm, M.: Calcium Exchange of the Intestine in Experimental Hyperthyroidism, J. Clin. Investigation **18**:763, 1939.

53. Moore, C. V.; Arrowsmith, W. R.; Welch, J., and Minnich, V.: Studies in Iron Transportation and Metabolism: Observations on Absorption of Iron from the Gastrointestinal Tract, J. Clin. Investigation **18**:553, 1939.

the alkaline intestinal juices and certain reducing agents, the latter tending to reduce any trivalent iron to the ferrous form before the change to nonionizable salts has occurred. Iron is absorbed from the intestinal tract largely, if not entirely, as ferrous iron. The degree to which ferrous salts are assimilated would seem to depend on the capacity of the intestinal contents to reduce them. It is the consensus that absorption takes place largely in the upper portion of the small bowel, where the iron passes directly into the blood plasma and not to any extent into the intestinal lymph channels. The influence of achlorhydria and an abnormally increased intestinal rate on hemopoiesis is obvious with such a hypothesis.

Experiments by Hahn and his collaborators [54] on the fate of iron excreted in the urine, bile and feces of dogs given radioactive iron by vein are of interest. Except for a small initial excretion for a few days in the urine and feces, little of the iron administered was lost. The body controls its iron stores by absorption or lack of it rather than by the capacity to eliminate it. The authors consider that the evidence is overwhelming that the dog excretes iron with difficulty and in small amounts by means of the biliary and gastrointestinal tracts.

Further observations on the impairment of intestinal absorption in deficiency diseases are contributed by Erf and Rhoads,[55] who studied the absorption of aminoacetic acid from the gastrointestinal tract in patients with untreated sprue and pernicious anemia. In these patients aminoacetic acid appeared to be absorbed more slowly than was normal, although this abnormality was corrected by adequate liver therapy. Evidence of malabsorption was not demonstrable in patients with intractable diarrhea, severe refractory anemia or pernicious anemia in complete or partial remission. Curiously enough, however, the authors demonstrated poor absorption of this substance in 2 patients with cirrhosis of the liver.

An interesting therapeutic suggestion is found in the report of Curtis and Ballmer,[56] who apparently demonstrated that plain liquid petrolatum and two emulsified preparations of petrolatum and agar removed appreciable amounts of carotene from ingested food. Plain liquid petrolatum saturated at room temperature with carotene still removed carotene from ingested food, but in lesser amounts, whereas apparently saturation of liquid petrolatum with carotene at body temperature prevented any interference with absorption of this precursor of vitamin A.

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54. Hahn, P. F.; Bale, W. F.; Hettig, R. A.; Kamen, M. D., and Whipple, G. H.: Radioactive Iron and Its Excretion in Urine, Bile and Feces, J. Exper. Med. **70**:443, 1939.

55. Erf, L. A., and Rhoads, C. P.: The Glycine Tolerance Test in Sprue and Pernicious Anemia, J. Clin. Investigation **19**:409, 1940.

56. Curtis, A. C., and Ballmer, R. S.: The Prevention of Carotene Absorption by Liquid Petrolatum, J. A. M. A. **113**:1785 (Nov. 11) 1939.

Previous suggestions that the duodenum exerts a hormonal control of carbohydrate metabolism are apparently disproved by Loew, Gray and Ivy.[57] These investigators employed various preparations of pancreas-free extracts of intestinal mucosa and failed to demonstrate in unanesthetized dogs any effect on the level of blood sugar.

Secretion by the colonic mucosa has been studied by Wright, Florey and Jennings,[58] who have demonstrated that parasympathetic stimulation either by faradic current or by cholinergic drugs caused the appearance of a strongly alkaline fluid. It contained a proteolytic enzyme, chlorine and phosphate ions and appreciable amounts of calcium. Sympathetic stimulation did not excite any secretion. Narcotics greatly diminished the rate of secretion, and atropine inhibited it completely. The resting or atropinized animal has the ability to reabsorb this secretion completely.

An interesting effect of distention of the colon and stimulation of its nerve supply has been observed by Goldman and Ivy,[59] who demonstrated in dogs and monkeys that distention caused an inhibition in the flow of bile from the liver in the absence of active choleresis stimulated by bile acids. A similar response was noted following stimulation of the central end of the colonic, inferior mesenteric, superior mesenteric and pelvic nerves, indicating that this inhibition is of reflex origin, while section of the hepatic nerves prevented the aforementioned effects and actually was followed by an increase in bile flow.

Some new information and a good deal of confirmation of previous experimental and clinical findings are supplied by the experiments of Coffey, Mann and Bollman,[60] who studied the digestion and absorption of fat, protein and carbohydrate in the normal dog. Control experiments on standard diets, high carbohydrate, high protein and high fat diets were performed, with a careful analysis of the fecal residue. It was found that normal dogs utilize foodstuffs efficiently. The fecal excretion of fat varied from 2.1 to 4 per cent, most of which was fatty acids. The fecal nitrogen was found to be fairly constant in absolute amount, except for a variation roughly proportional to the bulk of the feces. When

57. Loew, E. R.; Gray, J. S., and Ivy, A. C.: Is a Duodenal Hormone Involved in Carbohydrate Metabolism? Am. J. Physiol. **129**:659, 1940.

58. Wright, R. D.; Florey, H. W., and Jennings, M. A.: The Secretion of the Colon of the Cat, Quart. J. Exper. Physiol. **28**:207, 1938.

59. Goldman, L., and Ivy, A. C.: The Effect of Distention of the Colon and Stimulation of Its Nerve Supply on the Flow of Bile from the Liver, Ann. Surg. **110**:755, 1939.

60. Coffey, R. J.; Mann, F. C., and Bollman, J. L.: I. Fecal Residue of Fat, Protein and Carbohydrate in the Normal Dog, Am. J. Digest. Dis. **7**:141, 1940; II. The Effect of the Exclusion of Bile on the Absorption of Foodstuffs, ibid. **7**:143, 1940; III. The Influence of the Pancreas on the Utilization of Foodstuffs, ibid. **7**:144, 1940; IV. Substitution Therapy in Experimental Pancreatic Deficiency, ibid. **7**:149, 1940.

calculated as percentage of the protein of the diets used, the fecal nitrogen increased as the amount of dietary protein decreased. With low protein diets as much as 50 per cent of the nitrogen intake may be excreted in the feces. Carbohydrate excretion in the feces was only slightly affected by the diet, varying from 1 to 3 per cent. The exclusion of bile from the duodenum by an operative procedure, with resultant obstructive jaundice, still permitted utilization of over 50 per cent of large and moderate amounts of ingested fat. The feeding of a low fat, high protein diet was accompanied by utilization of over 70 per cent of the ingested fat. Only with a diet low in fat was there a preponderance of neutral fat in the feces. Nitrogen excretion under these conditions was definitely increased, and the recovery in the feces of 180 per cent of what was originally contained in a high fat diet offers striking evidence of loss of nitrogen from the intestinal canal, which appears to be proportional to the bulk of the feces and independent of the protein content of the diet. Utilization of carbohydrate was unaffected by the absence of bile. Pancreatectomy or the production of a complete pancreatic fistula resulted in an immediate loss of utilization of fat and carbohydrate, and an increased excretion of fecal nitrogen was noted, which was related to the increased bulk of the feces. It was less when diets rich in protein were employed. Evulsion of the pancreatic ducts was followed by a much more gradual failure of food utilization and appeared to parallel the degenerative changes occurring in the acinar tissue of the pancreas. Incomplete pancreatic fistulas or incomplete evulsion of the pancreatic ducts produced no detectable alteration of food utilization and indicated that only very small amounts of external pancreatic secretion are necessary to maintain complete digestion. Replacement therapy definitely reduced the loss of carbohydrate in the feces when large amounts of carbohydrate were included in the diet. Pancreatic juice, raw pancreas or pancreatin was effective, but only when given in very large amounts. Concomitantly with the improvement of carbohydrate utilization, the bulk of the feces was decreased and the amount of nitrogen reduced, but there seemed to be no direct effect of the replacement therapy on the amount of fecal nitrogen. In some experiments it appeared that slight improvement in fat utilization occurred when carbohydrate utilization was nearly at normal levels as the result of replacement treatment. The failure of replacement therapy was in marked contrast to normal utilization of foodstuffs when but small amounts of pancreatic juice drain into the intestine, as in animals with incomplete fistulas.

Numerous investigations have been made of the physiologic effects of various drugs on the alimentary tract and for the most part are in agreement. Because of the widespread clinical use of most of these preparations, it is thought advisable to review briefly the results of these pharmacologic studies. Although certain of the investigative findings

are by no means new, they offer confirmation of previous work, and inspection of the entire group of drugs may prove of interest and value. This is particularly true, for example, as drugs commonly employed in the preoperative and postoperative care of patients have either a strong motor or a strong inhibitory influence on the tone and on the peristaltic activity of the gastrointestinal tract. Anesthetic agents undoubtedly are in part responsible for some of the late, as well as the immediate, postoperative symptoms—nausea, vomiting, distention and gas pains.

Bisgard and Johnson,[61] like others, showed that the administration of morphine sulfate to man caused a marked increase in tonus in both the stomach and the small bowel. In the stomach there was an increase in the frequency and amplitude of peristaltic contractions, but in the small bowel a diminution of their amplitude was observed. In dogs, simultaneous observations were made on the stomach, the ileum and the colon and showed that there was an immediate increase in gastric tone and muscular activity, which persisted for about two hours. Gastric contractions greatly diminished in both frequency and amplitude for as long as six hours. Both the small bowel and the colon showed similar effects, namely, increased tone and diminishing motor activity, but in both there there was an early return to normal. Myers[62] studied the effect of morphine sulfate, diacetylmorphine and some related alkaloids in cats. The majority of the experiments showed a decrease in tone and in frequency and amplitude of movements of the digestive tract, although some animals showed an increase in gastric tone and activity following the use of morphine. Codeine sulfate produced variable results, at times a reduction and in other instances a slight increase in gastric tone and amplitude of movements being noted, but these were slight and short lived as compared with those produced by morphine or by diacetylmorphine (heroin). The effects of dilaudid hydrochloride on the stomach were far from constant, most animals showing an immediate relaxation of the stomach, with a decrease in the amplitude of the movements. The effects of dihydrocodeinone bitartrate (dicodid) on the stomach resembled those of codeine and consisted in a small, gradual increase in tone, followed by a relaxation to a subnormal level. Eukodol (dihydro-oxycodeinone) produced somewhat similar effects. All of the aforementioned drugs appeared to produce constant effects on the pyloric sphincter, namely, an increase in the tone of the sphincter accompanied

61. Bisgard, J. D., and Johnson, E. K.: The Influence of Certain Drugs and Anesthetics upon Gastrointestinal Tone and Motility, Ann. Surg. **110**:802, 1939.

62. Myers, G. N.: The Effects of Morphine, Diacetylmorphine and Some Related Alkaloids upon the Alimentary Tract: I. Stomach and Pylorus, J. Hyg. **39**:375, 1939; II. Small Intestine and Ileo-Colic Sphincter, ibid. **39**:391, 1939; III. Cecum and Colon, ibid. **39**:512, 1939.

with an increase in the amplitude of rhythmic movements. Dilaudid hydrochloride appears to be approximately eight times more active than morphine on the pylorus, while diacetylmorphine (heroin) is about one and a half times more potent than morphine. The effects of these three drugs last several hours, in contrast to the effects of codeine, dihydrocodeinone bitartrate (dicodid) and dihydro-oxycodeinone hydrochloride (eukodol), which are of short duration and slight degree. On the small intestine the effects of morphine were similar to those mentioned, namely, increased tone and peristaltic movements. Similar effects were noted after the use of dihydrocodeinone, codeine and dihydro-oxycodeinone, but in diminishing degrees. Morphine appeared to increase the tonus and movements of the ileocolic sphincter. Reagan and Puestow,[63] investigating by direct observation the motility of isolated segments of a dog's colon, produced evidence that morphine increases the tonus, frequency and strength of colonic contractions. The observation of diminishing effects of morphine and related alkaloids on the lower levels of the gastrointestinal tract is in agreement with the work of most previous investigators.

Seconal (sodium propylmethylcarbinylallylbarbiturate) was found by Bisgard to have no effect on the motor activity of the dog's stomach but was markedly inhibitory to the ileum and colon. The tone in both the small and the large bowel was markedly reduced, and muscular activity of the large bowel was almost entirely abolished, although the ileum continued to contract with normal frequency. The results of administration of evipal (C-C-cyclohexenyl-N-methyl-barbituric acid) were observed by the same author in man and in dogs. Evipal administered intravenously to man caused an immediate reduction in gastric tone and, with complete loss of consciousness, total abolition of motor activity, which returned promptly as complete consciousness was regained (after approximately thirty minutes). In the dog similar effects were noted, except that in the ileum rhythmic contractions continued with diminished amplitude although peristalsis was abolished. The action of atropine sulfate was noted by Bisgard in man and in dogs. After subcutaneous administration in man, there was a marked diminution of tone and of frequency and amplitude of contractions for approximately one and a half hours in both the stomach and the small bowel. For about thirty minutes peristalsis was entirely abolished in the ileum. In the dog the drug caused only relaxation and diminution of activity in the colon. When it was combined with morphine the two drugs counteracted each other,

63. Reagan, R. E., and Puestow, C. B.: The Activity of Isolated Segments of the Colon of Dogs, with Special Reference to the Influence of Certain Drugs, Surgery **6**:663, 1939.

so that the motor effect of morphine and the inhibitory effect of atropine resulted in essentially no demonstrable effect on gastric motility. Myers, in experiments on cats, noted that atropine modified the effects of morphine by producing a decrease in the tone and movements of the small bowel for varying periods, but subsequent injections of morphine during the period of atropine inhibition produced a further increase in tone and motility. He also noted that atropine abolished the effects of morphine and its related alkaloids on the tone and peristaltic movements of the cecum and colon, although according to Reagan the drug had little, if any, effect on colonic motility when observation was made on isolated segments of the colon. During intubation studies of the small intestine and the colon combined with fluoroscopic study of human subjects, Elsom and Drossner [64] also observed definite and prolonged effects on the small bowel and colon following therapeutic doses of atropine and belladonna. These effects consisted in a marked decrease in tone and peristaltic activity and a less striking effect on rhythmic contractions. This is entirely in keeping with clinical observations but is at variance with the work of some previous investigators.

The effect of syntropan (the phosphate of 3-diethylamino-2,2-dimethylpropylester of tropic acid), one of the newer antispasmodics, was studied by Clark and his collaborators.[65] In unanesthetized dogs intramuscular administration of the drug produced relaxation of gastric tone and inhibition of peristaltic activity, but only a weak inhibition of gastric secretion excited either by histamine or by meat was observed as compared to that obtained by the use of atropine. Duodenal motor activity was depressed, with less effect on the heart rate, size of the pupils and salivation than followed the use of atropine. The effect on excised segments of small intestine from rabbits and cats depended on the dose employed. In small amounts it effectively antagonized the stimulation produced by cholinergic drugs without muscular depression, but large amounts produced actual muscular depression. About one hundred times more syntropan than atropine was required to produce the same degree of depression of the intestine. In the unanesthetized dog syntropan antagonized the stimulating effect of acetylbetamethylcholine (mecholyl) morphine and pitressin to a far greater extent than did an equivalent dose of atropine, when the drug was administered by the intramuscular route. The effect of trasentin (diphenylacetyldiethylaminoethanol

64. Elsom, K. A., and Drossner, J. L.: Intubation Studies of the Human Small Intestine: The Effect of Atropine and Belladonna on the Motor Activity of the Small Intestine and Colon, Am. J. Digest. Dis. **6**:589, 1939.

65. Clark, B. B.; Shires, E. B. S., Jr.; Campbell, E. H., and Welch, C. S.: The Action of Syntropan on the Gastrointestinal Tract, J. Pharmacol. & Exper. Therap. **66**:464, 1939.

hydrochloride), another synthetic substitute for atropine, was observed by Necheles and his associates.[66] In the unanesthetized dog intramuscular administration of the drug in effective doses abolished or diminished gastric hunger contractions. In anesthetized dogs it diminished or abolished the muscular spasm and contractions of the stomach and of the small and the large bowel produced by various drugs or by vagal stimulation. Clinical trial of the drug by Spier, Neuwelt and Necheles[67] afforded some evidence that it offers occasional relief to patients suffering from ulcer or an irritable colon when orthodox therapy fails. Three patients with symptoms due to hypertrophic gastritis, unrelieved by other forms of therapy, received complete relief after use of the drug, and it controlled postoperative diarrhea in 5 patients previously refractory to usual medication (except camphorated tincture of opium). The authors concluded that the drug has a definite antispasmodic effect, clinical as well as experimental, its action on the small bowel probably being dependent on slowing down of intestinal motility and lowering of tonus, with restitution of a more normal intestinal gradient. Bisgard and Johnson, like other observers, found that glyceryl trinitrate administered sublingually produced in man and dogs a striking diminution of tone and peristaltic activity in the stomach and in the ileum. Complete abolition of parasympathetic activity was not obtained, the effect of the drug lasting approximately twenty minutes. In 2 patients, hunger contractions previously induced by the administration of dilute hydrochloric acid were abolished by glyceryl trinitrate.

Histamine given intravenously to anesthetized dogs with Thiry-Vella fistulas was found by Wolff[68] to cause a depression of gastrointestinal tone and motility. This is distinctly at variance with preceding observations, in which a definite increase in tone and motility and in unanesthetized dogs a complete lack of any effect have been noted by some observers. Acetlycholine, on the contrary, produced a definite increase in tonus and motility of the gastrointestinal tract, although here again Wolff's findings are in disagreement with several previous observations. Wolff's observations on the results of administration of acetylcholine are in keeping with those of most observers and are confirmed by the work of Necheles and Masur, who also showed that constant intravenous injection of small amounts of acetylcholine in dogs is followed by a

66. Necheles, H.; Neuwelt, F.; Steiner, N., and Motel, W. G.: The Study of a New Spasmolytic Drug: Diphenylacetyldiethylaminoethanol-Hydrochloride (Trasentin), Am. J. Digest. Dis. **6**:39, 1939.

67. Spier, E.; Neuwelt, F., and Necheles, H.: Clinical Study of New Synthetic Spasmolytic Drugs: Diphenylacetyldiethylaminoethanol, Am. J. Digest. Dis. **6**: 387, 1939.

68. Wolff, L. H.: The Effect of Certain Parenterally Administered Drugs on the Colon of the Dog, Am. J. Digest. Dis. **6**:243, 1939.

hemorrhagic condition of the upper parts of the gastrointestinal tract, namely, the stomach, duodenum and jejunum.

The injection of hypophysin was shown by Myers to cause in cats an immediate but temporary abolition or diminution of peristaltic movements and a loss of tone due to administration of morphine and its alkaloids. Wolff, in his experiments on dogs, noted a definite decrease in tone and motility following the use of solution of posterior pituitary, a confirmation of previous findings. This, however, is entirely unlike the effect noted in human beings, in whom invariably an increase in the motility of the colon is to be observed following injection of solution of posterior pituitary. Pitressin administered subcutaneously was noted by Bisgard and Johnson to cause a great increase in both frequency and amplitude of gastric peristalsis but no change in tone. After a preliminary lessening of tone and activity, both were markedly increased in the ileum, and the amplitude of the rhythmic contractions was diminished. The effect was rather short in duration. In the dog the drug exerted no influence on gastric motility and caused only an increase in tone in the small bowel. In the large bowel both tone and peristalsis were definitely increased, but, as in man, the duration of the effect was relatively short. Administered intramuscularly, pitressin was noted by Reagan and Puestow to cause an increased tonus in the colon of the dog, without any particular effect on motility. Elsom, Glenn and Drossner [69] investigated the action of the drug on the small intestine and the colon in human beings by means of intubation and fluoroscopy and noted an increase in motor activity. Usually both tone and peristaltic activity were augmented; in some instances, however, the peristaltic increase was associated with a decrease in intestinal tone. After a brief contraction of the duodenum prolonged after-relaxation was observed. In general, the effects of pitressin were most intense in the most distal portion of the tract, the activity in the ileum and colon at times bearing a roughly reciprocal relation. Necheles and Masur [70] noted that constant intravenous injection of moderate amounts of pitressin in dogs was followed by a hemorrhagic condition of the entire gastrointestinal tract, especially of the lower part of the ileum and the colon. Such a finding would be entirely in keeping with any prolonged increase in muscular tone and contraction and, incidentally, is of interest in view of the hypothesis advanced by Lium as to the mechanism underlying mucosal hemorrhage

69. Elsom, K. A.; Glenn, P. M., and Drossner, J. L.: Intubation Studies of the Human Small Intestine: The Effect of Pitressin and of Amphetamine (Benzedrine) Sulphate on the Motor Activity of the Small Intestine and Colon, Am. J. Digest. Dis. **6**:593, 1939.

70. Necheles, H., and Masur, W.: Gastro-Intestinal Pathology in Dogs Following Administration of Acetylcholine and Pitressin, Am. J. Digest. Dis. **6**:389, 1939.

and ulceration in colonic diseases. Wolff, in his experiments, noted a decrease in the tone and motility of the colon when the drug was injected intravenously, but his findings seem to be at variance with those of most investigators. Wolff also noted similar results from intravenous injection in dogs of preparations of pitocin but produced striking increases in tone and motility by use of physostigmine.

Prostigmine when administered intramuscularly to dogs was found by Reagan and Puestow always to produce uniform maximum contractions, varying from a marked increase in tonus to a state of tonic contraction. Of all the drugs used, prostigmine gave the most uniformly strong contractions. Wolff noted that intravenous injection of epinephrine caused a decrease in tone and motility of the colon in dogs, and Myers, experimenting on cats, also observed that administration of the drug caused a temporary inhibition both in the small bowel and in the ileocecal region following morphine stimulation. A similar decrease in the tone and motility of the dog's colon was noted by Wolff after intravenous administration of ephedrine. By fluoroscopic determination of the gastric emptying time for healthy adults, Van Liere and Sleeth [71] found that fluidextract of ergot caused an average delay of 30 per cent in the emptying time of the stomach and that ergotamine tartrate had a similar but less marked action. It was felt that the delay in gastric emptying was due to a direct influence on the gastric musculature by the drug rather than to any action on the autonomic nervous system.

The effect of anesthetics on gastrointestinal motility has been studied in some detail. In man, Bisgard noted a marked reduction in tone, with a complete reduction of gastric peristalsis. In the ileum rhythmic contractions continued, but with a diminution in both frequency and amplitude. At the end of twenty-four hours the contractions of the stomach were still smaller than normal. Within one hour after return of consciousness, however, there had developed an abnormally increased degree of muscular activity in the ileum. In the dog, during the induction of anesthesia there was a definite and marked increase in the muscular tone and the amplitude of contractions in both the stomach and the bowel. With the onset and during surgical anesthesia, a marked reduction of tone and cessation of motor activity were noted, except in the ileum, where again both rhythmic and tonic contractions continued, although they were relatively feeble. Both tonic and motor activity were slowly reestablished with return of consciousness. The colon and ileum promptly showed an abnormally increased tone, which was still evident twenty-four hours after return of consciousness, and twelve hours elapsed

71. Van Liere, E. J., and Sleeth, C. K.: The Effect of Fluid Extract of Ergot and of Ergotamine on the Emptying Time of the Human Stomach, J. Pharmacol. & Exper. Therap. **67**:250, 1939.

before the stomach had reestablished normal activity. The effects of ether preceded by a preliminary medication with morphine and atropine were noted in 2 patients during exploration of a retroperitoneal tumor in 1 and appendectomy in another. After the observation of irregularly increased tone and muscular activity during the stage of excitement, the tone gradually lessened but throughout remained elevated above the preanesthetic level. Motor activity was much diminished, but, although the ileum continued to contract with normal frequency, there was a great reduction in amplitude, which persisted throughout the period of observation (three hours). In the dog, the effect of ether anesthesia, as observed in the previous experiments, was definitely altered by premedication. The colon relaxed and ceased to contract as it did under the influence of ether alone, but in both the stomach and the small bowel premedication definitely delayed the return of normal activity.

In man, nitrogen monoxide and oxygen were noted to cause greatly but irregularly increased contractions of the stomach as regards frequency and amplitude, and the tone was moderately increased. The gastric tone remained slightly elevated after the anesthesia was discontinued. Motor function was reestablished slowly but was still subnormal three hours later. In the dog, during anesthesia the reactions were the same as those noted in man. After anesthesia was discontinued, the stomach continued to contract rapidly and violently, and this was concomitant with retching. Activity in the ileum and in the colon was almost completely abolished, and tone was diminished for thirty minutes. Normal function was reestablished in the stomach and ileum in one hour and in the colon in approximately two hours, but a record made eight hours after anesthesia showed increased activity in all three organs. The administration by inhalation of nitrogen monoxide, oxygen and ether to dogs showed results quite similar to those following the use of nitrogen monoxide and oxygen alone. The effects of cyclopropane were observed in man, and inhalation anesthesia by this method caused an increase in tone and rhythmic contractions but an inhibition of peristalsis during surgical anesthesia. Immediately on return of consciousness there was a diminution of tone to a subnormal level and a return of normal motor activity, which continued during observation periods for as long as three hours. In the dog, administration of cyclopropane induced an increase in tone and activity in the stomach and ileum, but decreased tone and activity were noted in the colon during surgical anesthesia. After cessation of anesthesia the colon reestablished and retained, during an observation period of six hours, normal tone and activity; the stomach and the ileum did likewise. Observations were made on the effects of cyclopropane when used as a supplement to a basal anesthesia induced by avertin with amylene hydrate. In man some diminution of motor activity was observed in the colon following use of avertin with

amylene hydrate. With the addition of cyclopropane, gastric tone and activity were temporarily increased, but without establishment of complete surgical anesthesia the tone and activity became relatively normal. Incidentally, there was noted to be a moderate degree of hyperacidity forty-eight hours after recovery from the anesthesia. In the dog no appreciable effect was produced by avertin with amylene hydrate, alone or supplemented by cyclopropane.

The use of spinal procaine hydrochloride anesthesia without premedication was studied during the course of several appendectomies in human beings. With the procaine hydrochloride, ephedrine was administered subcutaneously. During anesthesia the stomach showed a slight reduction of tone and a greatly diminished muscular activity. With the return of sensation there developed normal tone and motor hyperactivity. The contractions were exaggerated both in frequency and in amplitude, and this state continued for at least seventy-two hours after operation. The ileum, on the contrary, showed increased tone, with a slight reduction of all motor activity during anesthesia. The tone receded with the return of sensation and remained relatively normal. The rhythmic contractions showed increased amplitudes, and peristalsis was diminished as to both frequency and amplitude. In the dog, spinal anesthesia following administration of procaine hydrochloride resulted in a slight diminution in gastric motor activity and muscle tone. There was an increase in both the tone and the motor activity of the small bowel in 1 dog; other animals showed little or no change in the colon.

In dogs administration of oxygen and carbon dioxide resulted in an increase in the tone and frequency of contractions of the stomach, ileum and colon but a decrease in the amplitude. Normality was established when administration of oxygen was discontinued. Administration of carbon dioxide alone resulted in a reduction of tone and an irregularly increased motor activity of the entire gastrointestinal tract. The authors suggest that the influence of an individual anesthetic on the gastrointestinal tract may be dependent on its effect on the relative quantity of oxygen in the blood or tissues during anesthesia. When inhaled, oxygen stimulates and carbon dioxide inhibits gastric motor activity.

Reagan and Puestow noted that intravenous infusion had little, if any, effect on the motility of the dog's colon, but, like other observers, they found (as did Wolff) that concentrated solutions of sodium chloride (10 to 20 per cent) produced a marked increase in tonus and in the number and strength of contractions. They were able to produce an increase in colonic motility following intravenous use of 5 per cent dextrose solutions, although the effect was of short duration. Contrary to the usual finding of intestinal relaxation following use of intravenous calcium salts, Wolff noted that in the dog's colon there was an increase in both tone and motility.

CLINICAL ASPECTS

Esophagus.—The clinical aspect of esophageal disease is amply covered in an extremely informative review by Bird.[72] This author calls attention to recent advances in esophageal disease, particularly from the surgical point of view, in about eighty pages of carefully prepared matter. In spite of the fact that Bird's article is written primarily for surgeons, it represents a complete survey of the subject and should be read by any who are interested in esophageal disorders. The article not only reviews the current literature but makes it especially complete by reference to the observations of well known authorities throughout recent years. This is of particular value, as many of the conditions mentioned are rarely seen except by a few physicians whose work is almost entirely limited to this particular field. Congenital defects, such as tracheoesophageal fistulas with atresia, idiopathic obstruction, congenitally short or long esophagi, benign and malignant tumors, foreign bodies and their complications, traumatic lesions, strictures due to corrosive agents, esophagitis, peptic ulcer and specific infections are all treated in complete detail. The review is particularly timely because of important recent advances in surgical technic whereby a transthoracic approach is making possible results hitherto unattainable. A full description of the newer instruments and a detailed discussion of the technic and indications for esophagoscopy and bougienage are included.

Of particular importance at present is the full discussion of the various carcinomatous lesions of the esophagus, with a complete description of the symptoms, diagnostic methods and therapeutic approach. Bird indicates the extent to which Fischer's prophecy in 1923 has been fulfilled, namely, that "not many years from now many cures will have been accomplished in a disease that was beyond help and hope." Statistical studies based on all available figures from the United States and the Continent indicate that cancer of the esophagus as a cause of death is numerically very important. The value of adequate radical surgical treatment of this condition is emphasized by reference to the observations of Watson, who noted that autopsy studies show that carcinoma of the esophagus often remains to the end a localized disease. Scattered reports on radiation therapy are still extremely disappointing, and, although to date surgical cures are rare, there seems every reason for a more optimistic attitude toward this disease in the near future. A separate report by Engelstad [73] on the radiologic treatment of carcinoma of the

72. Bird, C. E.: Recent Advances in Surgery of the Esophagus: Congenital Defects, Surgery **6**:617, 1939; Carcinoma, ibid. **6**:772, 1939; Hemorrhage from Esophageal Varices, ibid. **6**:949, 1939.

73. Engelstad, R. B.: Radiological Treatment of Carcinoma of the Esophagus, Acta radiol. **20**:469, 1939.

esophagus stresses the present inadequacy of such therapeutic measures. This author reports the results of treating 119 esophageal carcinomas in the Norwegian Radium Hospital during the years 1932 to 1938. A permanent cure was not obtained in any case, and the average duration of life after treatment was only five months. Bird's review contains an excellent summary of the results obtainable by esophagoscopy, including the experiences of Jackson and others, and he does not fail to comment fully on the important diagnostic contributions by various roentgenologists, such as Macmillan, Moore, Schatzki and others.

A discussion of achalasia of the cardia is especially interesting, as this is a condition which rarely requires surgical intervention. Much of the history of the present knowledge of this condition is given in detail, including results of animal experimentation, the important clinical and histologic observations of Hurst and others on the degeneration of Auerbach's plexus and a consideration of medical and operative procedures. It is of interest that in such a surgical review the importance of medical treatment is so carefully stressed, and the article includes a discussion of the use of some specific medications. Bird points out the important fact that atropine and belladonna do not appear to be beneficial in the treatment of achalasia, although they do seem to be of benefit in cases of spasm of the esophagus at higher levels. The use of the nitrites is passed over, an unfortunate omission, as these preparations at times are of extreme value in controlling the symptoms of this curious condition. The value of instrumentation with dilation is thoroughly covered, and a resort to surgical measures is advocated only for chronic conditions which fail to respond to nonsurgical methods. An additional surgical approach to the therapy of this condition was stressed in a recent article by Chaikin,[74] who advocated bilateral cervicothoracic sympatheticoganglionectomy. Such a procedure, of course, is a logical one in view of the experimental work of Knight and others on the production of cardial achalasia. The results following such treatment should still be subject to close scrutiny, and the procedure should at present be considered highly experimental. To return to a consideration of Bird's article, one cannot commend too highly this full and carefully written review of an important subject.

A much shorter but also carefully prepared commentary on the more common esophageal disorders, with illustrative cases, is that of Darrow,[75] and some additional articles warrant brief notice. The Plummer-Vinson syndrome is dealt with in several articles, which contain nothing new but

74. Chaikin, N. W.: Modern Concepts of Cardiospasm, Rev. Gastroenterol. **6**: 332, 1939.

75. Darrow, C. H.: Lesions of the Esophagus, Rocky Mountain M. J. **36**: 306, 1939.

emphasize the important features of this curious condition. Good descriptive summaries are to be found in an article by Gerlings [76] and in an editorial in *The Journal of the American Medical Association*.[77] The clinical features of the condition are described in full detail, with adequate reference to the nutritional deficiencies, especially that of lack of iron, as of fundamental importance. The two articles stress one important point that should be noted, namely, the relation between this disease and cancer. Special reference is made to the observations of Ahlborn, who stated that in Sweden, at least, the Plummer-Vinson syndrome in women is a highly important factor predisposing to cancer of the mouth, pharynx and upper portion of the esophagus. He noted that 90 per cent of the women seen in Radiumhemmet for postcricoid cancer reported symptoms like those of the Plummer-Vinson syndrome. It is obvious from such observations that careful examination of the mouth and tongue is of diagnostic and therapeutic importance when considering the symptom of dysphasia, as well as in many other conditions.

One experimental study is of interest with reference to the cause of the Plummer-Vinson syndrome. Cordray [78] carried out careful histologic examinations of 12 laboratory mice in which severe anemia was produced by administering for five and a half months a diet including milk and all the essential vitamins but extremely low in iron. At the end of this time the animals were extremely weak and definitely underweight. They were then killed, and sections of the esophagus were carefully studied. Microscopic examinations revealed that the esophageal epithelium showed marked hyperkeratinization and proliferation of the cells comprising the epithelium. There was an increase of mitotic figures over the usual normal number, suggesting a definitely precancerous type of lesion. No fibrous tissue replacement in the musculature was evident, which conclusively ruled out esophageal "webs," a condition long held by Mosher to be the cause of the disease under discussion.

Schmidt [79] discusses spasm of the lower half of the esophagus as seen in a small group of cases at the Mayo Clinic. He indicates the important fact that such a condition, even with characteristic roentgen findings, may be entirely a reflex disorder secondary to extraesophageal disease and comments on the important fact that emotional disturbances

76. Gerlings, P. G.: Changes at Mouth of Esophagus in Plummer-Vinson Syndrome (Dysphagia with Anemia), Nederl. tijdschr. v. geneesk. **84**:1289, 1940.

77. The Plummer-Vinson Syndrome and Cancer, editorial, J. A. M. A. **113**: 1814 (Nov. 11) 1939.

78. Cordray, D. P.: The Plummer-Vinson Syndrome, Ann. Otol., Rhin. & Laryng. **49**:160, 1940.

79. Schmidt, H. W.: Diffuse Spasm of Lower Half of the Esophagus, Am. J. Digest. Dis. **6**:693, 1939.

alone can precipitate spasm of the distal portion of the esophagus in certain persons. The advantageous use of amyl nitrite, morphine sulfate, stramonium and papaverine hydrochloride is discussed.

An article by Vinson [80] on the management of benign stricture of the esophagus summarizes this condition particularly well and makes two important comments on its accurate diagnosis. In order that stricture at the pylorus may not be overlooked, roentgen examination of the stomach should be made for all patients who have swallowed a large amount of corrosive substances. Vinson properly warns against roentgen studies, however, until after the lumen of the esophagus has been restored by the passage of sounds. A second warning, of equal importance, lies in his statement that gastroscopy is seldom necessary in the management of benign stricture of the esophagus and adds particularly to the risk of treatment.

Kelly [81] has continued his previous observations on the mechanism of ascending fibrosis of the esophagus in infants. Observations on sections taken at different levels of the esophagus were made on autopsy material removed from 17 children dying under 1 year of age. Islets of gastric mucosa were found at all levels of the esophagus, from the level of the cricoid cartilage to and below the diaphragm, although in this particular group they were found most frequently at the upper end of the esophagus. In cases in which these islets of gastric tissue were not ulcerated, no fibrosis was to be noted. Following ulceration, however, an inflammatory reaction ensued around the ulcer, which at times involved all the coats of the esophagus. A chronic inflammatory reaction was at times localized and at times spread widely up and down the entire tube. This spreading inflammatory reaction preceded the fibrosis. The cellular inflammation bore a striking resemblance to some forms of this condition occurring in the adult, although in later life fibrosis under such circumstances is most unusual.

Because of the increasing use of the esophagoscope and the gastroscope, the report by Jemerin and Coleman [82] is of importance. These authors report 2 instances of formation of periesophageal cervicomediastinal abscesses following nonperforative instrumental trauma to the esophagus. The trauma was insignificant, such as may occur at any well conducted esophagoscopic examination. These cases indicate that such a complication should, therefore, be looked for after any esophagoscopy if pain, dysphagia or fever follows passage of the instru-

80. Vinson, P. P.: Management of Benign Stricture of Esophagus, J. A. M. A. **113**:2128 (Dec. 9) 1939.

81. Kelly, A. B.: Ascending Fibrosis of Esophagus and Its Relation to the Presence of Islets of Gastric Mucosa, J. Laryng. & Otol. **54**:621, 1939.

82. Jemerin, E. E., and Coleman, L. L.: Cervicomediastinal Abscess Due to Non-Perforative Trauma to Esophagus, J. Thoracic Surg. **9**:11, 1939.

ment. The authors believe that the sequence of events in their cases was probably as follows: Some degree of trauma to the esophagus took place, possibly with mucosal stripping and devitalization of the underlying esophageal wall by pressure. The devitalized tissue comprised a favorable nidus for anaerobic infection, with subsequent localized esophagitis, which spread through to the contiguous periesophageal tissue. It was possible on suspecting the complication to demonstrate small loculations of air in the periesophageal tissue, a roentgen finding pathognomonic of esophageal perforation, and in those instances in which no perforation could be demonstrated, these collections of air were probably due to the formation of gas by anaerobic bacteria.

A case of a most unusual condition, congenital tracheoesophageal fistula without atresia of the esophagus, is reported by Imperatori.[83] The case is remarkable in that such a condition is unusual without resulting atresia and still more so because of the plastic closure and apparent cure of the condition after eight years of life, with numerous operative procedures and infections of the respiratory tract due to aspiration.

The complex symptoms arising from diaphragmatic hernia are becoming more and more familiar to the members of the medical profession, and the diagnosis of the condition is becoming more precise with the use of more careful roentgen technic. Harrington[84] reviews the results of surgical treatment in a large group of cases and stresses the multiplicity of symptoms arsing from this condition, which simulates other organic diseases in the thorax or abdomen. An excellent histologic account of hiatus hernia is also given by Guthrie and Jones,[85] who similarly stress the importance of recognizing the condition frequently in order to avoid needless operations for suspected abdominal lesions or the placing of serious restrictions on a patient whose symptoms are thought to be due to cardiac disease. In many instances, diaphragmatic (hiatus) hernia is discovered accidentally in the course of routine but careful roentgen examination and is not the cause of any symptoms, thus resembling diverticulosis. The possibility of such a lesion being the cause of symptoms simulating those of cholelithiasis or coronary heart disease, however, must be continuously borne in mind. The report of Schiro and Benjamin[86] on severe microcytic anemia associated with diaphragmatic hernia contains one interesting

83. Imperatori, C. J.: Congenital Tracheoesophageal Fistula Without Atresia of the Esophagus, Arch. Otolaryng. **30**:352 (Sept.) 1939.

84. Harrington, S. W.: Diaphragmatic Hernia: Results of Surgical Treatment in Two Hundred and Ten Cases, California & West. Med. **50**:399, 1939; **51**:27, 1939.

85. Guthrie, D., and Jones, F. H.: The Frequency and Diagnosis of Hiatus Hernia, Ann. Surg. **111**:971, 1940.

86. Schiro, H. S., and Benjamin, J. E.: Severe Anemia Associated with Diaphragmatic Hernia, Ohio State M. J. **36**:164, 1940.

fact, that the patient was 1 of 3 sisters all of whom had diaphragmatic hernias, and the authors comment on the fact that a review of the literature on this condition suggests that the associated anemia not infrequently encountered is caused by congestion of the gastric mucosa proximal to the site of constriction and stated that in their case this could not be confirmed by gastroscopic examination. As a matter of fact, careful esophagoscopic or gastroscopic study of the larger hernial sacs will almost always reveal marked congestion of the gastric mucosa and frequently diffuse hemorrhagic points.

The report of Feldman [87] on the occurrence of peptic ulcer of the lower portion of the esophagus in asociation with hiatus hernia is of interest because of the fact that in each of 2 cases the ulcer was demonstrable by a careful roentgen technic. The occasional superficial mucosal erosions to be seen by careful esophagoscopic study usually occur in the hernial sac rather than in the esophagus and are not demonstrable by roentgen examination.

Traumatic herniation of the diaphragm with displacement of the abdominal viscera into the thoracic cavity is a well recognized condition, but the diagnosis is not always immediately considered. Articles by Brandt,[88] Falk and Smith [89] and Bliss and Green [90] bring out certain important clinical features. Brandt, in discussing the chronic form of a traumatic diaphragmatic hernia, provides illustrations of two types: a herniation which constantly causes symptoms, and the type in which there is postponement of symptoms for a long time after the original trauma, until incarceration may suddenly cause severe symptoms. He stresses the fact that a person may remain free from symptoms between the time of the injury and the appearance and signs of incarceration. Folk and Smith discuss the acute form of traumatic diaphragmatic hernia and also point out two variations: first, that observed in patients who have acute intestinal obstruction due to an acute or subacute traumatic hernia and, second, that observed in severely ill patients who present multiple injuries and extreme surgical shock at the outset and in whose cases it is proper at times to consider the possible existence of acute herniation of the viscera through the diaphragm in addition to the other existing injuries. Successful treatment depends on confirmation of such a condition by adequate roentgen study and by

87. Feldman, M.: Peptic Ulcer of the Lower Esophagus Associated with Esophageal Hiatus Hernia, Am. J. M. Sc. **198**:165, 1939.

88. Brandt, H.: Clinical Aspects in Diagnosis of Chronic Traumatic Hernias of the Diaphragm, München. med. Wchnschr. **86**:1312, 1939.

89. Falk, R., and Smith, R. S.: Acute Traumatic Diaphragmatic Hernia, Northwest Med. **28**:378, 1939.

90. Bliss, R. W., and Green, M. M.: Traumatic Rupture of the Diaphragm with Bilateral Pneumothorax, Southwestern Med. **23**:366, 1939.

immediate treatment. Such a case is that reported by Bliss and Green, in which a patient sustained a traumatic rupture of the diaphragm with bilateral pneumothorax following a serious accident. Successful treatment followed careful roentgen examination, including studies made after a barium sulfate enema, which revealed the transverse colon well up into the left thoracic space, and after a barium sulfate meal, which showed the stomach to be located in the left thoracic cavity.

Moore [91] outlines in detail the types of treatment made available by proper use of the esophagoscope. Briefly he outlines these as: dilation of strictures; cleaning out of pulsion diverticula prior to operation; removal of foreign bodies, and dilation for cardiospasm. A possible further use which may be available to the trained esophagoscopist is indicated in a report by Moersch,[92] who repeated the work of Franchner and Crofoord, of Stockholm, and successfully injected esophageal varices in a patient who had associated cirrhosis of the liver. This form of therapy has been considered by various clinicians, but Moersch is the first one in the United States to attempt such a maneuver successfully. Sufficient time has not elapsed since the report was published to permit determination of the efficacy of the injection treatment, but the author is to be congratulated on his patience and skill in projecting a form of therapy that may conceivably lead to a more successful attack on the problem of hematemesis from varicose veins in the esophagus.

Stomach.—Gastroscopy properly continues to attract the increasing attention of all physicians. Little new has been added in the past year, but at present the almost universal use of the gastroscope in various parts of the world has led to greater familiarity with the potentialities of this means of investigation. Fortunately, it has at the same time brought forth the beginnings of a critical evaluation of its usefulness, gastroscopists up to the present time having for the most part contented themselves with describing variations in the appearance of the stomach, as to both color and form. The actual number of observations on what constitutes normal variation in the appearance of the gastric mucosa is still far from adequate. Undoubtedly marked alteration in contour and general appearance occur during the various decades of life and follow acute or chronic constitutional diseases. These variations, in all probability, have no clinical implications from the point of view of symptomatology. There is still justification for skepticism in the interpretation of the chronic entity gastritis. Undoubtedly, pathologic changes exist in the stomach that can be

91. Moore, P. M., Jr.: Esophagoscopy: Treatment of Lesions of the Esophagus, Cleveland Clin. Quart. **7**:52, 1940.

92. Moersch, H. J.: Treatment of Esophageal Varices by Injection, Proc. Staff Meet., Mayo Clin. **15**:177, 1940.

identified by the gastroscopist but are in no way productive of symptoms. As Alvarez points out,[93] such alterations are entirely comparable to so-called chronic cholecystitis, "chronic appendicitis" and, under certain circumstances, peptic ulcer. A lack of knowledge exists regarding the exact histologic condition of the mucosal and submucosal tissues of the stomach accompanying the changes noted by the gastroscopist. Until such information is available, it will still be wise to regard gastroscopy as an important contribution to the study and diagnosis of disease of the stomach by a procedure which still must be utilized clinically with a good deal of caution. A similar conservative attitude is expressed by Browne.[94]

Rodgers[95] discusses the practical indications for gastroscopy and reviews the opinions generally accepted at present. Unfortunately, this author makes one statement which will not bear critical judgment, namely, that in cases of anemia the use of the gastroscope is of interest but of little practical value. As a matter of fact, the gastroscope may well throw a great deal of light on the type of process occurring with various types of anemia and may help to differentiate cases of primary deficiency disease, of which the associated gastric atrophy is an important indication. It is in these cases, which are by no means infrequent, that atrophy of the stomach should properly be designated by the term gastric atrophy rather than by the more commonly used but incorrect term atrophic gastritis, there being no evidence of a primary inflammatory reaction.

The actual danger incident to use of the gastroscope has been reviewed by Schindler,[96] who questioned sixty gastroscopists throughout the United States. On the basis of these questions he was able to establish the existence of only 1 fatality directly due to gastroscopy in the course of over 22,000 examinations. In addition to this fatality, there were 8 perforations of the stomach and 1 perforation of the jejunum in a resected stomach. All 9 patients recovered, either after conservative treatment or after surgical intervention. Schindler's inquiry also revealed the occasional danger inherent in the use of pontocaine hydrochloride as a preliminary preparation to the gastroscopic procedure. Apparently this drug is definitely dangerous when used in the presence of open mucosal wounds or on the mucosa of the the trachea and the bronchi. Three deaths following use of the drug had been reported in cases of carcinoma, and Schindler himself reported

93. Value of Gastroscopy Today, editorial, Am. J. Digest. Dis. **7**:51, 1940.

94. Browne, D. C.: Gastroscopy, New Orleans M. & S. J. **91**:533, 1939.

95. Rodgers, H. W.; Hartfall, S. H., and Lintott, G., in Discussion on Gastroscopy, Proc. Roy. Soc. Med. **32**:519, 1939.

96. Schindler, R.: Results of Questionnaire on Fatalities in Gastroscopy, Am. J. Digest. Dis. **7**:293, 1940.

1 case of an emaciated patient with stricture of the esophagus who had a bad reaction to the drug. He suggested that the drug should not be used for depleted patients but expressed the belief that ordinarily a dosage of not more than 2.5 cc. of a 2 per cent solution of the drug with epinephrine hydrochloride is safe. Any serious reaction should be treated at once by the intravenous administration of some such preparation as pentothal sodium.

One physiologic study of interest is that of Kirsner, Nutter and Palmer.[97] These authors investigated the hydrogen ion concentration of the gastric secretion after histamine stimulation in 72 patients with initial anacidity due to pernicious anemia, so-called atrophic gastritis, cancer of the stomach, irradiation of the stomach or one of a group of miscellaneous conditions, and made studies on the gastroscopic appearance of the mucosa in the same group of patients. They found no correlation between the hydrogen ion concentration of the gastric secretion, the presence or absence of a secretory depressant factor in gastric secretion, the presence or absence of anemia and the gastroscopic appearance of the stomach.

Phlegmonous gastritis is discussed by Cutler and Harrison,[98] who present 3 interesting case reports. The first case is of interest chiefly because it represents the usually accepted clinical picture of severe acute diffuse phlegmonous involvement of the stomach by hemolytic streptococci. Adequate surgical measures together with use of sulfanilamide and vitamin C were followed by recovery, a rare result with what is an almost universally fatal disease. The use of vitamin C was suggested because of the evidence of a little collagen formation in the granulative tissue removed at operation. The 2 other patients had localized areas of suppurative gastritis. In 1 patient there was pyloric stenosis due to an obstructive duodenal ulcer, and a biopsy specimen removed from the stomach at some distance from the pylorus revealed an area of suppurative local gastritis. Gastroenterostomy was performed for relief of obstruction, and recovery was uneventful. The last case was also one of chronic pyloric obstruction caused by a localized phlegmon of the gastric wall, the diagnosis being confirmed by biopsy material removed at the time of a pyloroplasty. The patient recovered and was well eight years later. The authors point out that it is of some importance to be cognizant of the fact that these two forms of suppurative gastritis occur.

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97. Kirsner, J. B.; Nutter, P. B., and Palmer, W. L.: Studies on Anacidity: The Hydrogen-Ion Concentration of the Gastric Secretion; the Gastroscopic Appearance of the Gastric Mucosa, and the Presence of a Gastric Secretory Depressant in Patients with Anacidity, J. Clin. Investigation **19**:619, 1940.

98. Cutler, E. C., and Harrison, J. H.: Phlegmonous Gastritis, Surg., Gynec. & Obst. **70**:234, 1940.

Consideration of chronic gastritis in its various forms has received the continued attention of numerous investigators,[99] all following the suggestion of Hurst and earlier students of the subject in stressing the possible etiologic importance of atrophic gastritis in relation to gastric cancer. Such a contention, although still incapable of being proved, is of real clinical importance and alone warrants the extensive use of the gastroscope for a careful continued observation of cases.

Schindler and Baxmeier[100] studied the mucosal changes of the stomach accompanying gastric ulcer and observed that 43 of 91 patients examined had no demonstrable gastritis and that in 10 others, in whom gastritis was not present at the first examination, it subsequently appeared. That gastritis might be associated with a gastric ulcer is not surprising, but the absence of any demonstrable gastric irritation, except for the localized ulcer, leads one to the conclusion that gastritis per se has little, if any, part in the causation of peptic ulcer of the stomach. Changes of the purpuric type were noted in almost half of the patients studied, but the exact significance of these changes is still far from clear.

Animal experiments carried out by Schindler, Necheles and Gold[101] on surgical gastritis are of interest as indicating the importance of surgically traumatized tissue during operation. Normal stomachs in which acid secretion had not been stimulated previous to the operation did not show gastric erosions or other significant pathologic changes after subtotal gastrectomy or some similar procedure, such as the use of clamps or the ligation of arteries. In the case of controls with the use of a stomach not operated on, stimulation of acid secretion of the stomach or artificial introduction of hydrochloric acid into the stomach did not per se produce any pathologic changes. On the contrary, those parts of the stomach which were deprived more or less completely of their blood supply for two hours and which were exposed to hydrochloric acid either by stimulation of gastric secretion or by introduction of hydrochloric acid into the stomach showed more or less intense ulceration, petechiae and hemorrhage. These changes were directly

99. Schindler, R.: Chronic Gastritis, Bull. New York Acad. Med. **15**:322, 1939. Schindler, R., and Gold, R. L.: Gastroscopy in Gastric Carcinoma Especially in Its Early Diagnosis, Surg., Gynec. & Obst. **69**:1, 1939. Jankelson, I. R., and McClure, C. W.: Present Status of Chronic Gastritis, Rev. Gastroenterol. **6**:473, 1939.

100. Schindler, R., and Baxmeier, R. I.: Mucosal Changes Accompanying Gastric Ulcer: A Gastroscopic Study, Ann. Int. Med. **13**:693, 1939.

101. Schindler, R.; Necheles, H., and Gold, R. L.: Surgical Gastritis: Study on Genesis of Gastritis Found in Resected Stomach, with Particular Reference to So-Called "Antral Gastritis" Associated with Ulcer, Surg., Gynec. & Obst. **69**:281, 1939.

proportional to the degree of anemia of the stomach and the degree of acidity prevailing in the resected part. That part of the stomach in which the blood supply was left intact and into which acid had been secreted after stimulation by drugs did not show any changes from the normal. These observations would seem to be extremely significant as offering at least a partial explanation of some of the postoperative changes following operations on the stomach.

Chronic idiopathic gastritis has also received considerable attention. That use of the term "atrophic gastritis" should possibly be open to a certain amount of criticism has already been suggested. The fact remains that many conditions exist that may properly be so classified. Schindler and Murphy [102] discuss in detail the symptoms of gastric disease characterized by diffuse atrophy of the gastric mucosa. They conclude that the digestive symptoms of this disease are not sufficiently characteristic to be of much diagnostic value. Among other symptoms, they characterize as extremely important soreness of the tongue and tingling of the extremities, and such a statement in itself justifies the foregoing criticism by the reviewer, as these symptoms are most commonly observed with deficiency conditions associated with macrocytic or microcytic anemia. However, the very indefiniteness and multiplicity of symptoms associated with true atrophic gastritis justifies Schindler's insistence on careful gastroscopic studies, particularly in view of the possible association of this condition with cancer.

That a fairly typical history of peptic ulcer may be obtained from patients who have no demonstrable ulcer but exhibit the gastroscopic appearances of gastric atrophy has been well recognized and is further established by the rather extensive clinical studies carried out by Morrison, Swalm and Jackson.[103] These authors also point out the not infrequent occurrence of hemorrhage and melena in these patients.

An excellent report of the results of liver and iron therapy in cases of atrophic gastritis not associated with pernicious anemia, combined cord degeneration, sprue or pellagra is that given by Schindler, Kirsner and Palmer.[104] Frequent but not invariable improvement followed institution of such therapy, as far as the gastroscopic appearance of the stomach and mucosa was concerned. It is of particular importance that in several instances discontinuance of liver therapy resulted in reappear-

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102. Schindler, R., and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis, Am. J. Digest. Dis. **7**:7, 1940.

103. Morrison, L. M.; Swalm, W. A., and Jackson, C. L.: A Frequent Nonulcerous Cause of the Peptic Ulcer Syndrome, Pennsylvania M. J. **43**:243, 1939.

104. Schindler, R.; Kirsner, J. B., and Palmer, W. L.: Atrophic Gastritis: Gastroscopic Studies on Effects of Liver and Iron Therapy, Arch. Int. Med. **65**: 78 (Jan.) 1940.

ance of gastric atrophy. Careful control observations in the absence of treatment were carried out, and in 1 case the subsequent sudden disappearance of gastric atrophy following a brief period of liver treatment certainly suggests a specific therapeutic result and adds fresh evidence to support the opinion that gastric atrophy in many cases is the result of true deficiency disease. A point of interest in this particular case is that free hydrochloric acid was found in the presence of extensive atrophy, although this is not surprising in view of the known fact that patients with proved pernicious anemia are rarely able to secrete moderate amounts of free hydrochloric acid. In addition to observations following the use of liver, the authors report 1 case of gastric atrophy associated with hypochromic anemia. There was marked improvement not only in the anemia but in a complete healing of the atrophic gastritis following iron therapy. These findings are in agreement with those reported by Chevallier and Moutier, Schiff and Goodman and others.

Further studies along similar lines are reported by Schiff and Goodman.[105] These authors present 5 cases of chronic gastric atrophy not associated with pernicious anemia, gastric cancer, protein deficiency or obvious vitamin C deficiency. The patients were treated with preparations of desiccated hog stomach (ventriculin). All showed marked symptomatic improvement, together with the disappearance of atrophic changes in the stomach. Administration of ventriculin was discontinued in the cases of 3 patients, 2 of whom showed a return of gastric atrophy and 1 an associated return of symptoms. A fourth patient showed definite improvement after discontinuance of the ventriculin, the atrophy recurring during ventriculin therapy, which would leave serious doubts as to the absolute specificity of this form of replacement therapy.

Entirely in keeping with most previous observations is the report of Johansen,[106] who followed 19 patients with pernicious anemia during liver therapy. In spite of clinical improvement and the disappearance of symptoms, at no time during a prolonged period of observation was there any change whatever in the achylia. Similar findings by other observers do not alter the fact that there is little, if any, association between the gastroscopic appearance of the stomach and the secretion or lack of secretion of hydrochloric acid. Such a conclusion has already been alluded to.

Sharp disagreement with the original findings of Jones, Benedict and Hampton and subsequent observations by Schindler, Chevallier and

105. Schiff, L., and Goodman, S.: Desiccated Hog's Stomach Extract (Ventriculin) in the Treatment of Atrophic Gastritis, Am. J. Digest. Dis. **7**:14, 1940.

106. Johansen, A. H.: Gastric Achylia in Pernicious Anemia After Liver Treatment, Ugesk. f. læger **91**:480, 1939.

Moutier is found in articles by Corey,[107] who claims that reestablishment of a normal-appearing mucosa or even an approximate return to normal was not seen in cases of pernicious anemia treated with liver. The findings of previous investigators, however, would seem to be well established and as much to be expected as the obvious and striking improvement commonly noted in the lingual atrophy after adequate treatment has been established.

Gastroscopic demonstration of intragastric foreign bodies is an obvious use of this method of investigation. Browne and McHardy [108] report several cases of phytobezoar, in which persistent digestive symptoms with inconclusive roentgen findings were explained by gastroscopic examination. An added report on the value of cytologic studies of the gastric contents is presented by Mulrooney.[109] One is rather skeptical, however, of the value of such a procedure in estimating the degree of gastric inflammation or progress due to therapy, especially in comparison with more precise methods of observation, such as careful roentgenographic and gastroscopic study or even adequate clinical observation.

Pyloric obstruction in infants is largely concerned with the condition known as hypertrophic stenosis. The condition is not infrequent and is well recognized by pediatricians. Several articles have appeared in the literature which stress certain important points of view regarding this particular disease. Terrien [110] points out the important fact that symptoms of pyloric stenosis can exist in the absence of true organic disease of the pyloric portion of the stomach, and this condition has been designated as pseudostenosis. The author alleges that as long as doubt exists and the general condition remains satisfactory, with maintenance of weight, it is advisable to be conservative and to restrict treatment to medical measures which aim particularly at preventing formation of an undigested residue in the stomach with accompanying gastric hypersecretion and spasm. He points out the apparently important diagnostic observation that the symptoms of pyloric stenosis in nurslings do not begin with birth; on the contrary, the attacks of vomiting appear after two, three or four weeks of normal development. The author claims that this lapse of time between birth and the appearance of symptoms, a so-called "free interval," is never missing in cases of stenosis. If there

107. Corey, J. B.: Gastroscopic Observations in Chronic Gastritis, Am. J. Digest. Dis. **7**:160, 1940; Gastroscopic Observations in Pernicious Anemia, Minnesota Med. **23**:311, 1940.

108. Browne, D. C., and McHardy, G.: Gastroscopy and the Phytobezoar: Report of Case of Diospyrobezoar, Arch. Int. Med. **65**:368 (Feb.) 1940.

109. Mulrooney, R. E.: Cytology of Gastric Contents in Reference to Gastritis, Proc. Staff Meet., Mayo Clin. **15**:81, 1940.

110. Terrien, F.: Pyloric Stenosis and Pseudostenosis in Nurslings, Presse méd. **48**:86, 1940.

is doubt, he concludes, particularly when evidences of malnutrition are noted, immediate surgical intervention is indicated.

The results of surgical intervention are discussed by Dijkhuizen,[111] who reports a mortality of 5.4 per cent in a series of 130 infants operated on by Romstedt's method of pylorotomy. Wyatt [112] records an even lower mortality (3 per cent) in a review of 100 similar cases. Attention is also paid to the medical treatment of this condition, which consists largely in replacement of fluid and chlorides and in adequate atropinization. Successful treatment has been noted on previous occasions, and Folsom [113] emphasizes the importance of atropine, insisting on the use of a fresh dilute solution, which makes possible the administration of several drops of 1 : 10,000, rather than 1 drop of 1 : 1,000, solution. Although most of the literature on this subject refers to surgical therapy, it is important that medical measures should not be overlooked, as their use may lead to favorable results. The marked reduction in mortality following surgical treatment of this form of pyloric stenosis is striking, and, as Wyatt points out, it has dropped in the last forty years from almost 100 per cent to a very low figure. There is little doubt that, in addition to increased skill in surgical technic, adequate attention to the restoring of fluid and the chloride balance has been of the utmost importance in securing such excellent results.

The preoperative and postoperative fluid treatment for pyloric stenosis is accurately discussed in an outline by Clausen and Ringsted,[114] and these authors quite properly include the use of supplemental transfusions of blood to prevent hypoproteinemia when large infusions of fluid are needed. A further observation on the postoperative care of infants who have undergone pylorotomy for hypertrophic pyloric stenosis is presented by Faber and Davis.[115] These authors noted the modifications of gastric peristalsis occurring after the Ramstedt operation and observed that there was a profound and prolonged depression of gastric motor activity, which lasted for about twenty-four hours, although in some instances it persisted for three or more days. In the average case, evacuation of material ingested soon after operation does not begin for

111. Dijkhuizen, R.: Surgical Treatment of Hypertrophic Pyloric Stenosis in Nurslings, Nederl. tijdschr. v. geneesk. **83**:5053, 1939.

112. Wyatt, O. S.:: Hypertrophic Pyloric Stenosis: Review of One Hundred Cases, Journal-Lancet **59**:233, 1939.

113. Folsom, T. G.: Pyloric Stenosis in Infancy, West Virginia M. J. **35**:416, 1939.

114. Clausen, J., and Ringsted, A.: Preoperative and Postoperative Fluid Treatment in Pyloric Stenosis, Acta chir. Scandinav. **82**:365, 1939.

115. Faber, H. K., and Davis, J. H.: Gastric Peristalsis After Pylorectomy in Infants, with Special Reference to Postoperative Care of Pyloric Stenosis, J. A. M. A. **114**:847 (March 9) 1940.

over eight hours and is not complete until twenty-four hours after operation. The authors believe that this peristaltic inactivity is closely related to postoperative vomiting, which is common and often persistent for several days after pylorotomy. For this reason they urge against the traditional administration of water and food during the first postoperative day.

The report of Knutsson and Rudburg [116] is of some interest. These observers make the interesting comment that pylorotomy performed for pyloric stenosis in children affects only the clinical condition. The roentgen appearance of stenosis persists for several years after the operation, in the absence of symptoms, and disappears only very gradually, as in the cases in which only medical treatment is given. Such a finding constitutes an additional reason for seriously considering the value of strictly medical treatment whenever possible.

Netto [117] reports 4 cases of a condition which he describes as achalasia of the pylorus in adults. Two of the patients had a megaesophagus and 1 a megacolon, the symptoms being dyspepsia, postprandial fulness, burning, eructations, nausea, vomiting and epigastric hyperperistalsis. Roentgen examination did not reveal stenosis of the pylorus, but because of the persistence of symptoms surgical intervention was advised, and at operation only abnormal thickening of the prepyloric antrum was found. This was due to hyperplasia of the muscle wall, and the author believes that the condition is identical to pyloric stenosis in the newborn except for the absence of a tumor. This lack in adults is attributed to generalized and uniform tissue hypertrophy. Microscopic examination of resected portions removed when a Finney pyloroplasty was done showed a pronounced loss of cells in the Auerbach-Meissner plexus, with replacement by true fibrous tissue. No typical characteristics of nerve trunk or ganglionectic cell degeneration were seen. In the absence of adequate roentgen data it is somewhat difficult to determine the indications for surgical treatment, but it is presumed that intractable symptoms persisting after adequate medical treatment were considered sufficient cause for abdominal exploration.

The pyloric stenosis associated with cholecystitis is fairly completely discussed by Baumel and Serre.[118] This, of course, is not a new entity, but it is sufficiently infrequent to warrant mention. The exact diagnosis is not always clear even after careful roentgen examination. The authors consider the evolution of symptoms, however, as important, two forms being distinguished: spasmodic stenosis, which as a rule responds

116. Knutsson, F., and Rudburg, S.: Roentgenologic Effect of Ramstedt's Operation in Pyloric Stenosis, Nord. med. (Hygiea) **4**:3101, 1939.

117. Netto, A. C.: Achalasia of Pylorus in Adults, Presse méd. **48**:148, 1940.

118. Baumel, J., and Serre, H.: Pyloric Stenosis of Cholecystic Origin, Arch. d. mal. de l'app. digestif **29**: 241, 1939.

to medical treatment, and stenosis in which the mechanical element of true obstruction predominates, which requires radical operation. A careful analysis of the patient's history, together with absence of signs of ulcer and cancer, constitute the chief diagnostic criteria. The authors are correct in saying that the prognosis is at times grave even with adequately planned surgical treatment.

A rather unusual type of pyloric stenosis is that due to a gallstone after perforation into the stomach. One such case is described by Segal and Morton.[119] Apparently because of large amounts of scar tissue in the pyloric and duodenal regions, the stone was unable to pass through the pylorus and eventually produced the picture of intermittent pyloric obstruction. Roentgen examination suggested that the lesion was located and fixed in the pyloric end of the stomach, but gastroscopic study revealed that there was a foreign body outside the antrum and free from the mucosa.

A rather complete study of many of the chemical changes encountered in the blood of patients with pyloric obstruction is presented by Noth and Wilbur.[120] A positive correlation between the amount of vomiting and the decreased values for blood urea and increased carbon dioxide–combining power was found, but the authors were unable to establish a definite relation between the values for these three chemical factors and the type of lesion present, the age of the patient, the amount of retained gastric secretion, the concentration of free hydrochloric acid in the gastric contents or a combination of any of these factors. They conclude that the low level of plasma chloride, while undoubtedly due to the loss of the chloride ion from vomiting, may be associated with other, additional factors. For practical purposes, they point out, the characteristic changes in the blood of patients suffering from pyloric obstruction are readily amenable in most cases to injection of physiologic solution of sodium chloride and 5 or 10 per cent dextrose.

Volvulus of the stomach, a rare clinical condition, is discussed in two papers. Singleton [121] describes 2 cases of persistent gastric volvulus and a third, in which the condition tended to recur, and discusses the clinical manifestations. He mentions the interesting fact that volvulus of as much as 180 degrees may be present without cardiac or pyloric obstruction or strangulation of the blood supply. Schatzki and Simione [122] also report a case and give an excellent discussion of the mechanical

119. Segal, H. L., and Morton, J. J.: Perforation of a Gallstone into the Stomach with Resulting Pyloric Obstruction: One Case Report with Gastroscopic and Surgical Findings, Am. J. Digest. Dis. **6**:720, 1939.

120. Noth, P. H., and Wilbur, D. L.: Chemical Changes in the Blood of Patients with Pyloric Obstruction, Ann. Int. Med. **13**:285, 1940.

121. Singleton, A. C.: Chronic Gastritis Volvulus, Radiology **34**:53, 1940.

122. Schatzki, R., and Simione, F. A.: Volvulus of the Stomach, Am. J. Digest. Dis. **7**:213, 1940.

abnormalities involved and an extremely clear sketch of the variations in gastric position encountered.

Diverticulosis of the cardiac end of the stomach, like diverticulosis of other portions of the gastrointestinal tract, may or may not be productive of symptoms. This important clinical fact is illustrated by a short report of Bonham [123] in a discussion of gastric diverticula, with an account of 3 cases in 1 of which the patient was completely relieved by operation, the patients in the other 2 being essentially free from symptoms with the simplest form of postural drainage. A curious manifestation of gastric diverticulosis is shown in a case reported by Halleron,[124] in which recurrent attacks of epigastric pain and jaundice without the appearance of a mass in the right upper quadrant were explained by a true diverticulum of the lower end of the stomach, which had become adherent to the under surface of the gallbladder and was intermittently the seat of an inflammatory reaction.

A discussion of gastric tumors other than cancer is of importance only for the purpose of emphasizing the fact that, although rare, they represent an appreciable number of benign or relatively benign invasions of the gastric wall. The symptoms are those of rather indefinite epigastric discomfort, but bleeding may be a feature. Suspicion and recognition of the possible existence of such tumors are of importance, because adequate surgical measures are frequently highly successful. Myhre [125] reviews the subject of benign gastric tumors, both epithelial and nonepithelial, and shows the extreme value of gastroscopic examination in the detection of these lesions, which are frequently difficult to demonstrate by roentgen examination.

A review of several articles [126] concerned with the various forms of sarcoma of the stomach reveals the diagnostic difficulties inherent

123. Bonham, D. T.: Diverticula of the Cardia End of the Stomach, Am. J. Digest. Dis. **7**:284, 1940.

124. Halleron, W.: Diverticula of the Stomach: Case Report, Minnesota Med. **22**:408, 1939.

125. Myhre, H.: Benign Gastric Tumors, Nord. med. (Norsk mag. f. lægevidensk.) **5**:282, 1940.

126. Taylor, E. S.: Primary Lymphosarcoma of Stomach, Ann. Surg. **110**: 200, 1939. Archer, V. W., and Cooper, G., Jr.: Lymphosarcoma of Stomach: Diagnosis and Treatment, Am. J. Roentgenol. **42**:332, 1939. Madding, G. F., and Walters, W.: Lymphosarcoma of the Stomach, Arch. Surg. **40**:120 (Jan.) 1940. Avent, C. H.: Primary Isolated Lymphogranulomatosis (Hodgkin's Disease) of the Stomach, ibid. **39**:423 (Sept.) 1939. Horsley, G. W., and Berger, R. A.: Leiomyosarcoma of the Stomach, Ann. Surg. **112**:22, 1940. Hubeny, M. J., and Delano, P. J.: Retothel Sarcoma of the Stomach, Radiology **34**:366, 1940. Chont, L. K.: Primary Sarcoma of the Stomach, ibid. **34**:714, 1940. Hochmann, A.: Sarcoma of the Stomach, Lancet **1**:362, 1940. Phillips, R. B., and Rivers, A. B.: Angiofibrosarcoma of the Stomach of Seventeen Years' Duration, Rev. Gastroenterol. **6**:468, 1939.

in these conditions. Treatment in individual instances must of necessity be surgical until the type of individual sarcoma and its identity have been established by microscopic examination. As the forms of lymphosarcoma constitute about two thirds of all sarcomas of the stomach, it is important that such studies be made in order to carry out adequate radiation treatment in addition to the necessary local surgical intervention. The prognosis of the combined group of lymphosarcomas is definitely better than that of carcinoma, leiomyosarcoma and fibrosarcoma. At least 1 case has been reported in which the patient lived for eight years after recognition of the gastric tumor. A report of a single case of angiofibrosarcoma of the stomach indicates the possible duration of symptoms with some of these rare conditions. In this particular instance the tumor was known to have been present in the epigastrium for seventeen years before surgical exploration took place. It is proper again to emphasize the important diagnostic help that may be obtained by skilful gastroscopic study in these cases, in which other diagnostic measures at present can offer little exact help.

The all-important subject of gastric carcinoma is, as usual, the basis of many communications. Animal experimentation on the possible etiology of malignant lesions of the stomach continues to be of interest. Although reports on the production of tumors of the stomach in experimental animals are very uncommon, Stewart [127] was able to produce squamous papilloma and squamous cell carcinoma of the stomach in a small percentage of mice in which an irritant in the form of methylcholanthrene in liquid petrolatum was injected into the anterior wall of the stomach. The time needed for the development of such tumors averaged about fourteen months, a fact which indicates that the mucous membrane of the stomach of the mouse is relatively resistant to the carcinogenic action of such an irritant as compared with other body tissues similarly treated. The adenomatous gastric lesion, which occurs spontaneously in mice of strain I, according to Andervont,[128] did not occur in mice of other strains kept in pens with strain I mice or fed specimens of the lesions. Dietary experiments on type I mice with such adenomatous changes in the stomach were carried out, with particular reference to avitaminosis A. The results obtained indicate that the lesion is not related in any way to the results of vitamin A deficiency. On the other hand, results obtained by Fridericia and his

127. Stewart, H. L.: Induction of Gastric Tumors in Strain "A" Mice by Methylcholanthrene, Arch. Path. **29**:153 (Feb.) 1940.

128. Andervont, H. B.: Studies on Some Possible Causative Factors of the Spontaneous Adenomatous Lesion of the Stomach in Mice of Strain I, Pub. Health Rep. **54**:2085, 1939.

collaborators[129] present fairly clear evidence that in rats subjected to a diet deficient in vitamin A, either intermittently or continuously, proliferative changes in the mucosal lining of the stomach were found in a much higher percentage (80 per cent) than in the control animals (18 per cent). The authors conclude that vitamin A deficiency must be in great measure a determining factor in the production of the gastric changes, although they admit that other factors, as yet unknown, also play an important part.

The possible influence of local gastric irritation on the formation of gastric tumors receives confirmation from the observations of Bonne and Sandground.[130] These authors report an epithelial tumor arising in the stomach of the common Javanese monkey, caused by a worm which lives in the depths of the tumor and has never been found free on the surface of the gastric mucosa. There is a constant association of the tumor and the worm. The tumor is a sharply localized, adenopapillomatous growth invading the submucosa, endothelial proliferation having been noted, with incipient invasion of the vessel wall. In 2 animals, found at a preliminary examination to be free of both tumor and worm, a tumor developed two and three months, respectively, after worms had been introduced into the stomach.

The generally accepted impression of the close relation between pernicious anemia and gastric cancer is substantiated by further observations reported by Jenner,[131] who studied the fate of 180 patients with pernicious anemia. The incidence of gastric cancer in this group was 4 per cent, and what appeared to be adequate and careful statistical and biometric studies in relation to other patients of the same age groups indicated that the incidence of cancer is well beyond the limits of accidental occurrence. Such a conclusion, although in no way new, is important because of the fact that the life expectancy of patients with pernicious anemia under present methods of therapy has been so much prolonged that the occurrence of other serious diseases must be constantly watched for.

The fact that the annual death rate from gastric cancer in the United States is somewhere between 30,000 and 40,000 gives sufficient indica-

129. Fridericia, L. S.; Gudjonsson, S.; Vimtrip, B.; Clemmesen, S., and Clemmesen, J.: Stomach Lesions in Rats Kept on Diets Deficient in Vitamin "A", Am. J. Cancer **39**:61, 1940.

130. Bonne, C., and Sandground, J. H.: On the Production of Gastric Tumors Bordering on Malignancy in Javanese Monkeys Through the Agency of Nochtia Nochti, a Parasitic Nematode, Am. J. Cancer **37**:173, 1939.

131. Jenner, A. W. F.: Pernicious Anemia and Gastric Carcinoma, Acta med. Scandinav. **102**:591, 1939.

tion of the need for continuous study on the subject. Rivers,[132] in a statistical study of 4,600 cases, emphasizes the fact that men seem to progress into a definite dyspepsia-cancer age from five to ten years earlier in life than women. In man this period seems to start in the late fifties. Because of this fact, he properly urges an exhaustive search for cancer in patients in whose cases "dyspepsia" is the major complaint, even when another, less formidable cause has been discovered.

With the improved technic of gastric surgery as it exists today, Bryan[133] states that between 20 and 50 per cent of early carcinomas of the stomach can probably be cured by operation and that roentgen diagnosis of early carcinomatous lesions is accurate in between 90 and 95 per cent of cases. Even if Bryan's figures are somewhat optimistic, there is no doubt that modern gastric surgery offers much greater hope for success than formerly, once the diagnosis has been established. There is equally little doubt that improvement in roentgen diagnostic technic has kept pace with progress in the surgical field. The figures for operability and successful resection of gastric cancer naturally vary according to the community in which the figures are obtained, depending not only on the diagnostic and operative skill of the local surgeons but on the education of the public and the various economic groups represented by patients admitted to hospitals in given districts. The percentage of five-year operative cures reported varies from 3 per cent to approximately 20 per cent of all cases in which resection of the tumor has been done. It is to be noted, however, that resection has undoubtedly been increased in the surgical program in the last few years. However, much remains to be accomplished from the point of view of early diagnosis. Even with the best statistical results, five-year cures of cancer of the stomach are equivalent to between 5 and 6 per cent of all cases in which operation is performed. Articles of interest in this connection are those by Rippy,[134] Walton[135] and Parsons and Welch.[136] A slight note of optimism is to be found in the article by the last-mentioned authors, who feel that the total number of diagnosed gastric cancers has increased greatly in recent years, that more patients have been operated on and that the percentage of resectable growths has increased, with a reduction in operative mortality.

132. Rivers, A. B.: The Importance of Cancer as a Cause of Chronic Dyspepsia, J. A. M. A. **113**:1188 (Sept. 23) 1939.

133. Bryan, W. E.: Carcinoma of the Stomach: An Analytical Study, J. Tennessee M. A. **32**:390, 1939.

134. Rippy, E. L.: Cancer of the Stomach: Conclusions from Study of Two Hundred Cases, South. Surgeon **8**:359, 1939.

135. Walton, J.: Carcinoma of the Stomach, Brit. M. J. **2**:1127, 1939.

136. Parsons, L., and Welch, C. E.: Curability of Carcinoma of the Stomach, Surgery **6**:327, 1939.

Attention has previously been called to the use of hydrochloric acid in preoperative preparation of patients with cancer of the stomach. Abramovich [137] reports the results of bacteriologic studies undertaken to determine the effect of this procedure, originally suggested by Friedrick in 1933. Studies on 64 patients with gastric achylia about to be operated on for gastric cancer showed that the anacid gastric contents were never sterile. Oral administration of a solution of 0.25 per cent hydrochloric acid over the course of several preoperative days destroyed certain types of micro-organisms and diminished the number of colonies of other types. Drinking of the solution, combined with lavage, accelerated the cleansing process, the maximum bactericidal effect being accomplished in from thirty to sixty minutes. Because of the fact that 70 odd per cent of the fatalities following operation for gastric cancer in the Leningrad Institute were due to peritonitis, the author suggests the value of such a procedure, especially if practiced immediately before the operation, as an important factor in reducing possible postoperative peritonitis.

Restoration of normal gastric tone and motility after subtotal resection has been studied by Vitkin.[138] This author made observations on a stomach resected by the Billroth II method or some modification of it. Satisfactory rhythmic evacuation occurred after a subtotal gastrectomy, and apparently normal gastric tone was restored after operation, regardless of whether the condition of the stomach preceding operation represented atony or hypertonicity. The type of evacuation obtained apparently does not depend on the extent of the resected region, as rhythmicity of evacuation was observed even in cases of almost total gastrectomy. There were no data which would substantiate belief in the formation of a sphincter in the region of the anastomosis. Spasm of the anastomosis after gastrectomy undertaken for cancer the author believes to be an early symptom of local recurrence. One interesting note in this communication is the observation that hyperplastic gastritis and jejunitis follow subtotal gastrectomy, but without any subjective manifestations. Whether such a statement is true in its entirety or not, it provides one further reason for a critical analysis of the significance of gastroscopic findings.

In view of the work of Bisgard, already alluded to, on the effect of barbiturates on gastrointestinal tone and motility, one is inclined to question the correctness of Romino's [139] observations, as he advocates

137. Abramovich, S. A.: Hydrochloric Acid in Preoperative Cleansing of Cancerous Stomach, Novy khir. arkhiv **42**:355, 1939.

138. Vitkin, S. F.: Motor Function of the Stomach After Resection, Ann. Surg. **111**:27-1940.

139. Romino, J. D.: Postoperative Vomiting and Phenobarbital, West Virginia M. J. **35**:461, 1939.

the use of phenobarbital in doses ranging from 3 to 5 grains (0.19 to 0.32 Gm.) on the day before operation. Except after what amounted practically to anesthetic doses, Bisgard was unable to demonstrate any effect of seconal (sodium propylmethylcarbinylallylbarbiturate) and evipal (C-C-cyclohexenyl-N-methyl barbituric acid) on motility and tone, and even after anesthetic doses there was only a transient abolition of both during the period of unconsciousness. Romino's impression that postoperative nausea and vomiting were distinctly diminished is of interest but should be substantiated by careful observations on a large control series before this form of medication is accepted as a routine preoperative measure.

Numerous pathologic rarities involving the stomach are reported but are of little interest except as curiosities. In the case of Baumann-Schenker [140] there was an unusual manifestation which is worthy of passing comment. The case described was one of cystoid pneumatosis of the stomach and jejunum, in which there was no spontaneous pneumoperitoneum. The diagnosis was established preoperatively on the basis of the roentgen appearance of the vesicular structure of the stomach, duodenal bulb and upper portion of the small bowel. The condition apparently was attributable to chronic ileus of long standing, and the multiple small submucosal cysts were not demonstrable even at operation until a biopsy specimen had been taken. The report of syphilis of the stomach by McPeak [141] is of interest chiefly because he not only presents the clinical, pathologic, gastroscopic and roentgen observations in a given case but is able to show progressive changes from early to extensive involvement of the stomach. Gastric tuberculosis is so rare that the report of Zelman [142] on the combination of tuberculosis of the pancreas and a proved tuberculous gastric ulcer warrants passing comment. That unsuspected rupture of the stomach may follow trauma is known, but such a possibility is not usually thought of. The note by Casberg [143] is therefore of interest in recalling such a possibility. In his case the patient presented the typical picture of a ruptured spleen, but at operation an unsuspected rupture of the stomach was found as well. Shellac bezoars are medical curiosities much less common than trichobezoars and phytobezoars. Inlow [144] reports a case in which the

140. Baumann-Schenker, R.: Pneumatosis cystoides ventriculi et jejuni, Acta radiol. **20**:365, 1939.

141. McPeak, C. N.: Syphilis of the Stomach, Am. J. Roentgenol. **43**:832, 1940.

142. Zelman, J.: Tuberculosis of the Pancreas and the Stomach, Am. Rev. Tuberc. **41**:809, 1940.

143. Casberg, M. A.: Traumatic Rupture of the Spleen and the Stomach, J. A. M. A. **114**:1544 (April 20) 1940.

144. Inlow, H. H.: Shellac Bezoars, Radiology **38**:618, 1940.

foreign body was diagnosed by roentgen examination and removed by gastrotomy. Chemical analysis established the composition of the bezoar. Shellac bezoars have been found only in male drunkards who have access to alcoholic shellac solutions.

Peptic Ulcer.—The literature on peptic ulcer continues without abatement. Any complete review of it is not justified, as a great deal of the material published is unimportant or contains no new point of view. Many of the articles consist in reiterations of previous clinical or experimental observations. As yet no specific etiology or therapy of this chronic intractable disease has come to light, although a certain amount of valuable information is constantly being added to the knowledge of the subject.

An article by Mann [145] is of value largely because it constitutes a review of the results of experimental investigation on the mechanism of peptic ulceration. He points out at least two mechanisms in the development of the experimentally produced ulcer. One involves initially a disturbance of the blood supply to the ulcerated region and is still not clearly understood. The second depends on mechanical and chemical factors, ulceration occurring only where the mucosa is exposed to acid gastric contents not protected by the normal mechanism for diluting, buffering and neutralizing the acidity. The actual site of the ulcer is determined by the mechanical factor of expulsion of gastric contents and occurs in the region where the gastric juice first strikes after emergence from the stomach. A third type of experimentally produced peptic ulcer comprises lesions produced by cinchophen. The entire life history of such ulcers has not yet been fully observed, but they appear to be a combination of the two types just described. The review is of particular importance because it summarizes the principles underlying the experimental approach to this difficult subject.

Fresh evidence of the possible relation of circulatory disturbances to the production of peptic ulcer in man is presented by Boles, Riggs and Griffiths,[146] who record careful histologic studies in 161 cases of acute focal lesions of the gastric mucosa. These authors concluded that, regardless of causation, focal gastric lesions are the result of chronic circulatory insufficiency to all the structures of the gastric wall. Such circulatory deficiency is part of a generalized insufficiency intensified by intrinsic vascular peculiarities, anatomic or vasomotor, of the stomach. The histologic preparations presented by these authors were excellently made and would seem to constitute important evidence in favor of at

145. Mann, F. C.: Mechanism of Peptic Ulceration: Review of Results of Experimental Investigation, Brit. M. J. **1**:707, 1939.

146. Boles, R. S.; Riggs, H. E., and Griffiths, J. O.: Role of Circulation in the Production of Peptic Ulcer, Am. J. Digest. Dis. **6**:632, 1939.

least one of the possible causative factors of ulcer. A further contribution to such a conception is that of Berg,[147] who was able by frequent injections of pitressin in normal vagotomized dogs to produce marked hypermotility of the stomach and eventually ulcerations, some of which extended into the muscularis. Although chronic ulcerations were not produced, the lesions were more extensive and more frequently found in those animals in which vagotomy had been performed. Berg feels that the results were strongly suggestive of the possibility that functional vascular alterations play an important role in the causation of ulcer.

A slightly different mechanism in the production of ulcer, but one also involving the circulatory system, is that noted in the animal experiments of Penner and Bernheim.[148] Previous necropsy studies of patients dying with ulcer suggested that ulceration of the gastrointestinal tract might be due to alterations in the vasomotor mechanism present in this condition. In the necropsy material ulcerative lesions were noted in the esophagus, stomach and duodenum, appearing postoperatively or following diabetic acidosis, in the absence of any systemic disease, such as diffuse vascular disease, chronic glomerulonephritis, periarteritis nodosa or any localized pathologic change in the stomach or duodenum. Examination of the necropsy material indicated that the earliest histologic changes consisted of marked distention of the capillaries and venules in the mucosa of the stomach and in the submucosa of the esophagus and the duodenum. Edema and focal hemorrhages were observed, due probably to increased permeability of the capillaries resulting from the stasis consequent to arteriolar constriction occurring in response to shock. Ultimate progression resulted in focal necropsy of the tissues involved. Because the authors felt that such vasomotor disturbances associated with shock constituted the basis for the ulcerations observed, they attempted to reproduce in animal experiments a pathologic picture similar to that noted in cases of shock. Repeated intraperitoneal injections of epinephrine were utilized, and the writers were able to observe the production of lesions in the digestive tract grossly identical to those observed in human material. These experimentally produced anatomic changes are offered as evidence in support of the clinical appearance of vasospasm which is of sufficient severity and duration to cause tissue necropsy. Such a mechanism may well be operative in cases of extensive burns known to be associated with acute peptic ulceration. One typical

147. Berg, M.: Experimental Studies on the Production of Peptic Ulcer by Vasomotor Alterations (Pitressin Episodes), Am. J. Digest. Dis. **7**:78, 1940.

148. Penner, A., and Bernheim, A. I.: Experimental Production of Digestive Tract Ulcerations, J. Exper. Med. **70**:453, 1939; Acute Postoperative Esophageal Gastric and Duodenal Ulcerations: A Further Study in the Pathologic Changes in Shock, Arch. Path. **28**:129 (Aug.) 1939.

case is reported by Keeley,[149] with a review of the literature on this subject.

The neurogenic origin of peptic ulcer is well recognized, and several case reports are to be found in the literature for the year, all verifying Cushing's observations and the original assumption of Rokitansky, who appears to have been the first to regard ulcerative processes of the gastrointestinal tract as of neurogenic origin. The exact mechanism operative in such cases still can only be surmised, however, and a detailed review of the case reports is not warranted in this article. Whether psychogenic factors (as has been indicated by certain writers) or neurogenic overstimulation from intracranial tumors effects the production of peptic ulcers by means of vasomotor disturbances is still open to wide speculation. An attempt by Ask-Upmark [150] to correlate the occurrence of peptic ulcer with existing hepatic disturbances incident to cirrhosis of the liver is of clinical interest but in no sense conclusive. In addition to noting 9 cases of gastric or duodenal ulceration among 22 patients who died from cirrhosis of the liver, the author performed a number of galactose tolerance tests on patients with peptic ulcer. He concludes that the frequency with which abnormality was noted, together with the behavior of the blood sugar curve, provides evidence of a causative relation between hepatic dysfunction and peptic ulceration.

A careful analysis of 75 cases of patients with proved peptic ulcer and of 72 other cases of persons known to be clinically allergic is of interest because of the conservative tone of the conclusions of the authors, Ehrenfeld, Brown and Sturtevant.[151] These writers conclude that allergy is not a significant factor in the production of peptic ulcer. They make the additional valuable point, however, that gastrointestinal symptoms suggestive of ulcer are not infrequent among allergic persons and that roentgen studies of such persons frequently show transient spastic phenomena in the stomach or duodenum. Such findings lend support to the explanation of Demel that gastrointestinal allergic manifestations may be due to localized wheals or to angioneurotic edema.

Further studies on the effect of pregnancy and administration of chorionic gonadotropin (antuitrin S) on experimental ulcer are presented by Farbman, Sandweiss and Saltzstein.[152] Neither pregnancy

149. Keeley, J. L.: Gastro-Intestinal Ulcerations Following Burns, Am. J. Surg. **45**:85, 1939.

150. Ask-Upmark, E.: Further Observations on the Pathogenesis of Peptic Ulcer, Acta med. Scandinav. **103**:280, 1940.

151. Ehrenfeld, I.; Brown, A., and Sturtevant, M.: Studies in Gastrointestinal Allergy; Allergy in Pathogenesis of Peptic Ulcer, J. Allergy **10**: 342, 1939.

152. Farbman, A. A.; Sandweiss, D. J., and Saltzstein, H. C.: The Effect of Pregnancy and of Antuitrin-S on Cinchophen Ulcers in Dogs, Am. J. Digest. Dis. **6**:702, 1939.

nor injections of gonadotropin had anything but a very slight effect on cincophen ulcers in dogs, a decidedly different result from that previously noted when chorionic gonadotropin was injected into Mann-Williamson dogs. Such a finding justifies the cautious note regarding parenteral therapy of endocrine preparations continuously sounded by Sandweiss and his associates.

The predictable effect of predigested food on experimental peptic ulcer in Mann-Williamson dogs was tested by Emery, Zollinger and Rutherford [153] in an attempt to control any nutritional deficiency which might be present. No beneficial results were obtained, although the authors feel that further similar studies are indicated because of previous experimental work done by Fauley and Ivy.

Increasing recognition of the fact that ulcers occur at an early age is evidenced by the appearance of numerous case reports, the youngest patient being described in the case noted by Hunter and Dryerre [154] of a duodenal ulcer in a 3 day old child. The vomiting of coffee-ground material and the appearance of melena were ultimately followed by death, and autopsy showed kissing ulcers in the duodenum. A review of the literature dating from Spiegelberg's original description (1869) of duodenal ulcer in the newborn and a discussion of possible causes are of interest.

The notation of peptic ulcers in rather unusual locations indicates the necessity for skilled roentgen observations to provide an exact demonstration of the site of peptic ulceration. Horsley [155] reports 2 ulcers proved to be exactly in the pyloric sphincter. Dimerleau [156] includes 4 instances and Brulé and his co-workers [157] a fifth instance of peptic ulceration of the second portion of the duodenum, while Berry and Dailey [158] add a case of primary ulcer of the jejunum. Routine roentgen study in such instances frequently misses lesions of this character, and it is only by persistent effort on the part of the roentgenologist and insistence by the clinician on the importance of ulcer-like symptoms that such unusually located ulcers are found. In the case of low duodenal and jejunal ulcers

153. Emery, E. S.; Zollinger, R., and Rutherford, R. B.: The Effect of Predigested Food on Experimental Peptic Ulcer, Surgery **7**:574, 1940.

154. Hunter, W., and Dryerre, H. W.: Duodenal Ulceration in New Born, Brit. M. J. **2**:15, 1939.

155. Horsley, G. W.: Ulcers of the Pyloric Sphincter with Case Reports, Virginia M. Monthly **67**:29, 1940.

156. Dimerleau, J.: Ulcers of Second Portion of Duodenum, Arch. d. mal. de l'app. digestif **29**:856, 1939.

157. Brulé, M.; Hilleman, P.; Gilbrin, E., and Callandry, L.: Ulcers of Second Portion of Duodenum, Arch. d. mal. de l'app. digestif **29**:846, 1939.

158. Berry, L. H., and Dailey, U. G.: Primary Ulcer of the Jejunum, Am. J. Digest. Dis. **7**:63, 1940.

it is important to restate the fact that the pain will continue to be periodic but will be localized, as a rule, in the periumbilical region.

The relation between benign and malignant gastric ulcers is extremely well summarized by Palmer.[159] Important points in differential diagnosis and the difficulties involved are thoroughly considered, including the results of all diagnostic procedures. Although there is no pathognomonic sign to indicate the benign nature of the lesion, Palmer insists that the total evidence available from a careful study permits clinical differentiation of benign and malignant gastric lesions to be made with a high degree of accuracy. Such a statement is undoubtedly correct but must be qualified by one of the opening sentences in his article, which bears repetition: "One must bear in mind that the accuracy of the clinical differentiation varies from person to person, just as the mortality rate from resection varies from individual to individual. Both depend upon the skill of the physician or surgeon." The article is well worthy of careful perusal.

Although originally skeptical of the conclusions of Holmes and Hampton regarding the frequency with which prepyloric ulcerations show malignant characteristics, Sampson and Sosman,[160] in a recent report, confirm in every way the importance of the former authors' observations. Their study is based on a series of 545 patients admitted to the Peter Bent Brigham Hospital, comprising all the patients with gastric ulcer and gastric cancer subjected to operation or autopsy during a twenty-five year period. Gastric ulcers in the prepyloric 1 inch (2.5 cm.) of the stomach were found to be cancerous in 75 per cent of cases.

Observations on large groups of patients with ulcer over reasonably long periods have been recorded by various authors, but nothing new has been added to the routine measures that are successfully used in controlling the symptoms and progression of peptic ulcer. It is obvious from the various reports that careful attention to a routine, which may be one of many, is capable of giving satisfactory results. Some of the newer therapeutic measures are worthy of comment, although conclusions resulting from their use are frequently open to criticism. The treatment of duodenal ulcer with intramuscular injections of histaminase by Nakada [161] recalls previous favorable reports on the results attributed to the use of histidine preparations. The favorable results reported are not subject to any control observations and should be considered with a great deal of frank skepticism. It is unfortunate that such reports creep

159. Palmer, W. L.: Benign and Malignant Gastric Ulcers: Their Relation and Clinical Differentiation, Ann. Int. Med. **13**:317, 1939.

160. Sampson, D. A., and Sosman, M. C.: Prepyloric Ulcer and Carcinoma, Am. J. Roentgenol. **42**:797, 1939.

161. Nakada, J. R.: Treatment of Duodenal Ulcer with Histaminase, Rev. Gastroenterol. **6**:389, 1939.

into the literature without adequate studies, as many patients suffering from such a chronic disease as duodenal ulcer are subjected to unnecessary or expensive forms of therapy without any ultimate realization of their original hopes for a cure. Trial of new methods should in no case be discouraged, but it is important to insist on adequate study of their use before favorable results are reported.

Metz and Lackey [162] continue to report favorable results associated with the use of posterior pituitary preparations. Intranasal insufflation of posterior pituitary powder, they claim, completely relieved symptoms in from seven to twenty-one days in 67 patients with ulcer. Coincidentally with the disappearance of symptoms, the authors noted a gain in the general feeling of well-being, with a diminution of nervousness and insomnia. No dietary regimen and no other medication was employed, and the patients remained ambulatory during treatment. That hormonal secretions, including those of the pituitary, exert a definite influence on gastric and duodenal motor and secretory physiology is known, but the authors are wise in stating that posterior pituitary preparations should be considered complementary to the accepted principles of management of peptic ulcer.

Although treatment of peptic ulcer with histidine preparations has largely fallen into disrepute, the data obtained by Schmidt [163] provide further evidence against the hypothesis that there is a histidine deficiency in patients with ulcer which prevents normal healing. From his figures it seems obvious that there is no appreciable difference between the histidine content of patients with peptic ulcer and that of normal persons.

In an attempt to prove the essential role of gastric acidity in the genesis and course of chronic ulcer, Palmer and Nutter [164] present a complete review of the literature since 1926. They admit that small acute and subacute gastric ulcers may occur in the presence of achlorhydria proved by histamine but cited statistical studies of over 1,000 cases of chronic gastric and duodenal ulcer in which no instance of chronic benign ulcer was observed in the presence of complete achlorhydria. They further refer to the failure of other observers to find chronic or acute peptic ulcers in over 1,700 autopsies of patients dying from pernicious anemia. Although it is undoubtedly true that typical peptic ulcer is extremely uncommon in the presence of histamine achlorhydria, it is difficult to disregard the findings of other careful

162. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Preparations, Am. J. Digest. Dis. **7**:27, 1940.

163. Schmidt, E. G.: The Histidine Content ("Diazo Value") of the Blood in Peptic Ulcer, J. Lab. & Clin. Med. **25**:512, 1940.

164. Palmer, W. L., and Nutter, P. B.: Peptic Ulcer and Achlorhydria: Further Study of Role of Acid Gastric Juice in Pathogenesis of Peptic Ulcer, Arch. Int. Med. **65**:499 (March) 1940.

observers, who occasionally have noted after adequate studies the existence of undoubted typical peptic ulceration in patients refractory to histamine stimulation. The article, however, is to be carefully considered as indicative of the role of gastric acidity as one of the important factors in activation of peptic ulceration of the stomach and duodenum. The possible corollary, to be inferred by some, that so-called neutralization of gastric acidity is the only physiologic and therapeutic approach to the medical treatment of peptic ulcer is one that will hardly bear acceptance, and in this regard it is of some importance to read Bloomfield's [165] timely comment on the problem of hyperacidity. The point of view to be found in this article is worthy of repetition not only as regards ulcer therapy but as concerns the broader aspects of the so-called clinical syndrome of hyperacidity.

In view of the foregoing statements, it is of interest to note the appearance of more articles questioning the necessity and value of too enthusiastic attempts to neutralize gastric acidity in cases of peptic ulcer. Both Nicol [166] and Ronald [167] point out the fact that healing of peptic ulcer and relief of symptoms can take place even though hyperchlorhydria is unaltered and agree that the importance of free acid in the stomach in interfering with the healing of ulcers has been overemphasized. Further skepticism as to the actual role played in the control of symptoms of ulcer by antacid therapy is voiced by Steigmann and Fantus,[168] who studied the efficacy of four currently used substances in the treatment of peptic ulcer: Sippy powder no. 1 (1 part calcium carbonate and 3 parts sodium bicarbonate), aluminum hydroxide gel, neutralized karaya gum and an acid-bismuth mixture. After use of these preparations, the authors pointed out that the relief of pain, which was uniform, must have been secured by some other means than an antacid action, most probably by lessening of gastric tension. Even Kirsner and Palmer,[169] in a study of the effect of various antacids on the hydrogen ion concentration of the gastric contents, agree that the most efficacious combination for a reduction of p_H values to the "proteolytic neutralization level" of Hollander is obtained by the com-

165. Bloomfield, A. L.: The Problem of Hyperacidity, Am. J. Digest. Dis. **6**:700, 1939.

166. Nicol, B. M.: Control of Gastric Acidity in Peptic Ulcer, Lancet **2**: 881, 1939.

167. Ronald, J.: Value of Therapeutic Measures in Duodenal Ulceration, Brit. M. J. **2**:1033, 1939.

168. Steigmann, F., and Fantus, B.: Acidity Modification Therapy in Peptic Ulcer, Am. J. Digest. Dis. **7**:197, 1940.

169. Kirsner, J. B., and Palmer, W. L.: The Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents, Am. J. Digest. Dis. **7**:85, 1940.

bined use of atropine and calcium carbonate. They believe that the effectiveness of atropine is apparently due to the resultant diminution in the amount of gastric secretion and the prolongation of gastric emptying time.

Deleterious effects of antacid therapy have long been recognized, and among them is the possible causation of renal stones by use of alkalis in the treatment of ulcer. An article by Kretschmer and Brown [170] indicates that stone formation in alkali-treated patients is only 1.8 per cent greater than in patients who do not receive antacid therapy. They consider this difference is insignificant and agree with the point of view that the specific cause of renal and ureteral stone is unknown. Such a statement, while true, does not take into account recent work, such as that of Higgins and Albright, on the dissolution of renal stones, and there is strong reason to believe that renal stones may be formed by excessive alkali therapy in a few patients who have preexisting renal damage. Eisele's [171] studies in this connection are of interest. He points out the great increase of work on the part of the kidney, with particular relation to an increased urinary excretion of solids, under alkali therapy.

The efficacy of aluminum hydroxide gel preparations in controlling symptoms of ulcer and in promoting healing continues to be reported by various observers.[172] There seems to be almost unanimous agreement that colloidal aluminum hydroxide administered either periodically or by continuous drip in connection with other generally accepted measures is of real value. Whitcomb,[172a] in comparing its use with that of a routine Sippy regimen, believes that it shortens hospitalization and gives more constant relief than that obtainable by other antacids. Emery and Rutherford [172b] are in agreement and cite as evidence of this the fact

170. Kretschmer, H. L., and Brown, R. C.: Do Alkalis Used in the Treatment of Peptic Ulcer Cause Kidney Stones? Study of 1,940 Cases, J. A. M. A. **113**:1471 (Oct. 14) 1939.

171. Eisele, C. W.: Changes in Acid-Base Balance During Alkali Treatment for Peptic Ulcer: Clinical Analysis of Alkalosis in Twenty-Eight Patients, Arch. Int. Med. **63**: 1048 (June) 1939.

172. (*a*) Whitcomb, B. B.: Results from Colloidal Aluminum Hydroxide in Peptic Ulcer Therapy: An Eighteen Month Survey at the Hartford Hospital, J. Connecticut M. Soc. **3**:272, 1939. (*b*) Emery, E. S., and Rutherford, R. B.: Further Studies on Treatment of Peptic Ulcer with Aluminum Hydroxide Gel, New England J. Med. **222**:205, 1940. (*c*) Woldman, E. E., and Polan, C. G.: Value of Colloidal Aluminum Hydroxide in Treatment of Peptic Ulcer, Am. J. M. Sc. **198**:155, 1939. (*d*) Steigmann, F.: Colloidal Aluminum Hydroxide "Continuous Drip" in the Treatment of Large Gastric Ulcers: The Therapeutic and Diagnostic Value of this Method, Illinois M. J. **76**:443, 1939. (*e*) Eads, J. T.: Clinical Results from the Continuous Intra-Grastic Drip Using Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. **7**:32, 1940.

that a group of patients previously intractable to other medical measures finally responded to prolonged administration of aluminum hydroxide. Use of the continuous drip method is still stressed by Woldman and others,[172c] particularly for patients who are refractory to healing and who have severe pain at night. There is little doubt that the aluminum hydroxide gel preparations constitute a permanent addition to the drug therapy of ulcer, the only disadvantage of their use being the tendency of such preparations to form fecal impactions. In addition to their action as antacids, it should be pointed out that administration of these preparations is followed by no subsequent increase in gastric secretion, such as may be observed following the use of certain alkalis, and, as is pointed out by Komarov and Komarov,[173] their antipeptic action appears to be as important both in vivo and in vitro as their action on gastric acidity. Komarov and Krueger [174] suggest, on the basis of Pavlov pouch experiments, that the use of colloidal aluminum hydroxide gel not only diminishes peptic activity by direct contact with the gastric juice in the stomach but causes a simultaneous diminution of peptic activity in a separate Pavlov pouch.[174]

The necessity for care in preventing the development of specific nutritional deficiencies during treatment of patients with peptic ulcer still needs to be stressed. Although it probably is of no etiologic importance, there is little doubt that many patients with ulcer are on diets seriously lacking in ascorbic acid, a point again emphasized by Warren, Pijoan and Emery.[175] Brown, Northrop and Metheny [176] report 3 cases of surgically treated ulcer, in all of which there were evidences of pellagra. It is obvious that such deficiencies should be not only recognized but thoroughly treated before abandonment of medical measures.

There seems to be no real lack of agreement as to the indications for surgical treatment of peptic ulcer. Modifications in technic are relatively unimportant, and the increasing and probably justifiable popularity of subtotal gastrectomy as a proper operative procedure when operation is indicated seems to be established on firm grounds. That subtotal gastrectomy offers the final surgical solution of the ulcer problem is still open to some doubt, although it undoubtedly represents

173. Komarov, S. A., and Komarov, O.: The Precipitability of Pepsin by Colloidal Aluminum Hydroxide, Am. J. Digest. Dis. **7**:166, 1940.

174. Komarov, S. A., and Krueger, L.: The Effect of Aluminum Hydroxide Gel on Gastric Secretion in the Dog, Am. J. Digest. Dis. **7**:190, 1940.

175. Warren, H. A.; Pijoan, M., and Emery, E. S., Jr.: Ascorbic Acid Requirements in Patients with Peptic Ulcer, New England J. Med. **220**:1061, 1939.

176. Brown, H. K.; Northrop, N. W., and Metheny, D.: Peptic Ulcer and Pellagra: Report of Three Surgical Cases, Northwest Med. **39**:101, 1940.

the most satisfactory approach as yet evolved. The comment of Knapper [177] is salutary. In a follow-up report on the surgical treatment of patients with duodenal ulcer he comments on the apparently successful results obtained but adds: "Since an interval of from 1 to 7 years does not permit a definite evaluation of the surgical results, the author intends to repeat the follow-up examinations after a few years." Such a point of view is distinctly healthy and indicates an honest skepticism of results which might be copied by many overenthusiastic surgeons. Finsterer [178] discusses the diagnosis and surgical treatment of juxtacardiac gastric ulcers in an article on the diagnostic and therapeutic difficulties associated with these lesions, which are fortunately rather rare.

The problem of gastrojejunal ulcer and gastrojejunocolic fistula is a serious one, and articles by Finsterer [179] and Walters and Clagett [180] illustrate the hazards, as well as the rationale, of surgical intervention for these distressing complications of primary gastric operations. As Walters and Clagett point out, diagnosis is usually not difficult, although it is not always possible to obtain precise roentgen evidence of the existence of the lesion. Evaluation of recurrent symptoms and knowledge of the previous gastric surgical procedures are nearly always adequate for diagnosis. A careful study of these articles is of importance to the internist as well as to those interested in gastric surgery. The fact that gastrojejunal ulcers rarely develop after an anterior gastroenterostomy is important. McPeak [181] describes 2 cases of benign duodenocolic fistulas, which are of interest as medical curiosities, there being only 2 other possible cases in the literature at present. The diagnosis may be missed if roentgen examination is limited to study after a barium sulfate meal, the condition in this respect resembling gastrojejunocolic fistulas, which frequently are demonstrated only after a barium sulfate enema.

The success of gastric surgical procedures frequently depends on detailed attention to postoperative nutritional needs, a point that is becoming more universally recognized by both surgeons and internists.

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177. Knapper, C.: Results of Modern Surgical Treatment of Ventricular (Duodenal) Ulcer, Nederl. tijdschr. v. geneesk. **83**:2058, 1939.

178. Finsterer, H.: Juxtacardiac Gastric Ulcer, Wien. klin. Wchnschr. **52**: 394, 1939.

179. Finsterer, H.: Recurrent Peptic Ulcers of Jejunum and Surgically Incurable Ulcers, Wien. Arch. f. inn. Med. **33**:296, 1940.

180. Walters, W., and Clagett, O. T.: Gastrojejunal Ulcer: A Study of One Hundred and Fifty-Five Cases, Am. J. Surg. **46**:83, 1939; Gastrojejunocolic Ulcer and Fistula, ibid. **46**:94, 1939.

181. McPeak, C. N.: Benign Duodenal-Colic Fistula, Radiology **34**:343, 1940.

Stengel and Ravdin [182] describe the maintenance of nutrition in surgical patients and append a description of the orojejunal method of feeding. Their article is of technical as well as of practical interest as a contribution to postoperative care. An interesting observation in this regard is that of Dennis,[183] who demonstrated by microscopic studies that definite injury to the mucosa of the entire jejunum and ileum can result from instillation of distilled water. The mucosa of this part of the alimentary tract normally is never exposed to hypotonic solutions, and their use under artificial conditions is not justified. These observations demonstrate the necessity for caution in using distilled water rather than isotonic solutions for irrigations of the small bowel as a clinical measure.

The question of hemorrhage in relation to peptic ulcer continues to attract considerable attention. A review of the entire subject of gastrointestinal hemorrhage by Eusterman and Morlock [184] presents an excellent summary of the subject, particularly from the point of view of the actual causes of hematemesis. In addition, these authors call attention to the importance of bleeding from otherwise symptomless lesions, such as duodenal ulcers, or from any of the other several causes of bleeding of the upper part of the gastrointestinal tract. They indicate the need for serious study of this particular phase of the problem in the following statement: "Whether the absence of pain is due to individual nonsensitivity or to certain anatomic and physiologic factors, such as the depth of the lesion, the degree of resulting visceral dysfunction, the extent of direct involvement of nerves or peritoneal tissue, or to a combination of these factors, has not been definitely determined." They also draw attention to the role played by unusual physical or mental stress in precipitating these silent hemorrhages. Such a consideration is known to be of importance, but additional evidence for it is presented by Davies and Wilson [185] and by Melton.[186] The former authors investigated a group of 75 patients recovering from acute perforations or from attacks of massive hemorrhage, and stress the fact that episodes of unusual emotional tension immediately preceded these complications in four fifths of the patients. Melton reports what appears to be the

182. Stengel, A., Jr., and Ravdin, I. S.: Maintenance of Nutrition in Surgical Patients with Description of Orojejunal Method of Feeding, Surgery **6**:511, 1939.

183. Dennis, C.: Injury to the Ileal Mucosa by Contact with Distilled Water, Am. J. Physiol. **129**: 171, 1940.

184. Eusterman, G. B., and Morlock, C. G.: Gastrointestinal Hemorrhage from Otherwise Symptomless Lesions with Special Reference to Duodenal Ulcer, Am. J. Digest. Dis. **6**:647, 1939.

185. Davies, D. T., and Wilson, A. T. M.: Personal and Clinical History in Hematemesis and Perforation, Lancet **2**:723, 1939.

186. Melton, G.: Hematemesis and the War, Lancet **1**:316, 1940.

direct effect of war strain in England as experienced in a single hospital, the incidence of admissions due to gross hemorrhage or perforation from ulcer actually doubling in the four months after the outbreak of hostilities over that noted in the preceding eight months.

The incidence and mortality of massive hemorrhage continue to be sources of interest and of statistical reports,[187] of which only general mention can be made in this review. There is general agreement that mortality from this complication increases rapidly after the middle of the fifth decade of life and that medical treatment is indicated, with rare exceptions. The adoption of appropriate medical measures for patients under the age of 45 appears to reduce the mortality to an almost negligible figure, and Meulengracht's latest report,[187d] of 10 deaths in a series of 491 patients with bleeding ulcers, is a very striking one. All agree that surgical intervention, either in the form of subtotal gastric resection or by transduodenal ligation of the bleeding vessel, should be resorted to only for patients in the older age groups and as an exceptional maneuver. The inclusion or exclusion of selected material still makes any critical analysis of statistical studies extremely difficult, but the preceding conclusions seem amply justified and are agreed to by most authors.

As to the details of medical treatment, there are naturally differences of opinion. With few exceptions, current articles agree that immediate feeding of a carefully prepared diet has no deleterious effects and is probably associated with real benefit to the patient from the point of view of shortening convalescence in the hospital and the period of recovery from the posthemorrhagic anemia as well as that of a possible immediate effect on the cessation of the hemorrhage. It is somewhat surprising to find that physicians like Andresen[187e] fear the use of properly administered transfusions as an almost routine measure in the treatment of massive gastric hemorrhage. Almost all careful observers agree that there is no appreciable rise in blood pressure after a transfusion given slowly by the gravity method and that such a procedure is

187. (*a*) Blackford, J. M., and Cole, W. S.: Massive Hemorrhage from Peptic Ulcer: A Study Based on Vital Statistics of the City of Seattle During Four Years and Personal Experience Based on Private Practice, Am. J. Digest. Dis. **6**:637, 1939. (*b*) Graham, J. G.; Alexander, J. C., and Kerr, J. D. O.: Hemorrhage in Peptic Ulcer: Review of Two Hundred and Forty-One Consecutive Cases, Lancet **2**:727, 1939. (*c*) Andresen, A. F. R.: Results of Treatment of Massive Gastric Hemorrhage, Am. J. Digest. Dis. **6**:641, 1939. (*d*) Meulengracht, E.: Medical Treatment of Peptic Ulcer and Its Complications, Brit. M. J. **2**:321, 1939. (*e*) Holman, C. W.: Severe Hemorrhage in Gastric and in Duodenal Ulcer: A Study of Ninety Cases, Arch. Surg. **40**:150 (Jan.) 1940. (*f*) Lanphere, G. H.: Recent Advances in the Treatment of Hematemesis and Melena, California & West. Med. **52**:59, 1940. (*g*) Jones, F. A.: Hematemesis and Melena: Observations on the Use of Continuous Drip Transfusion, Brit. M. J. **1**:915, 1939.

important, with its actual contribution of hemoglobin, plasma protein and prothrombin as well as its immediate effect on the restoration of blood volume.

Regeneration of blood and hemoglobin after massive hemorrhage appears to be determined in most instances by the degree of the anemia at the moment. It is of interest that two independent observers conclude that the rate of recovery from anemia may be nearly independent of the administration of food and iron. Graham, Alexander and Kerr [187b] noted a remarkable recovery of hemoglobin following a single massive hemorrhage without administration of iron, and Lyons and Brenner [188] observed that the rate of regeneration was fully as good in cases of bleeding treated by a strict Sippy regimen as that reported for cases in which a liberal puréed diet and iron had been employed. Transfusions seemed to have no effect on the rate of erythropoiesis.

In referring to the generally recognized salt and water requirements after massive hemorrhage, Jones [189] suggests that the dehydration observed in such cases may be due not only to loss of fluid and subsequent insufficient fluid intake but in part to forced diuresis resulting from increased excretion of urea. The existence of marked azotemia following massive hemorrhage has been attested to by various authors since its original description by Christianson and Longinnetti, but this factor has not been particularly recognized as of possible importance in stimulating diuresis and thereby increasing dehydration following hemorrhage. The exact mechanism responsible for producing such azotemia is still open to some doubt, and the results of studies reported by various writers [190] are not in entire agreement. That the rise in blood urea is due in part to actual absorption of nitrogenous material from decomposition of blood in the intestinal tract is fairly generally accepted. The statement that it is not associated with impairment of renal function, even though transient (Schiff and his collaborators [190a]), is open to real doubt. There is also no general agreement as to the exact prognostic significance of an

188. Lyons, R. H., and Brenner, C.: Erythropoiesis Following Bleeding Peptic Ulcer, Am. J. M. Sc. **198**:942, 1939.

189. Jones, F. A.: Hematemesis and Melena: Observations on Salt and Water Requirements, Brit. M. J. **2**:332, 1939.

190. (*a*) Schiff, L., and Stevens, R. J.: Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena, Arch. Int. Med. **64**:1239 (Dec.) 1939. (*b*) Stevens, R. J.; Schiff, L.; Lublin, A., and Garber, E. S.: Renal Function and Azotemia Following Hematemesis, J. Clin. Investigation **19**:233, 1940. (*c*) Demole, M., and Neeser, J.: Hyperazotemia in Digestive Hemorrhage, Gastroenterologia **64**:208, 1939. (*d*) Black, D., and Leese, A.: Nitrogen and Chloride Metabolism in Gastro-Duodenal Hemorrhage, Quart. J. Med. **9**:129, 1940. (*e*) Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastrointestinal Hemorrhage: I. General and Clinical Considerations, Am. J. Digest. Dis. **7**:189, 1940; II. Experimental Observations, ibid. **7**:191, 1940.

elevation of blood urea nitrogen. Schiff and others affirm that repeated estimations of blood urea in cases of hematemesis are indicated because of their prognostic significance and as an aid to therapeutic management, while others, e. g., Demole and Neeser,[190e] doubt that any such clinical significance is attached to the values. In all probability it will still be proper to consider the evidences of nitrogen retention associated with massive gastrointestinal hemorrhage as an interesting expression of physiologic disturbance rather than as a guide to clinical decisions or therapeutic measures.

An article by Daniel and Egan [191] is of incidental interest in this regard. These authors determined the approximate quantity of blood necessary to produce a tarry stool and conclude that the presence of at least 50 to 80 cc. of blood is needed in the gastrointestinal tract for the occurrence of such a phenomenon.

Many articles appeared during the year discussing acute perforation in cases of peptic ulcer. Most of them are surgical and contribute nothing new to an understanding of this particular complication of ulcer. Almost all writers agree that immediate operation is indicated, although it is known that occasionally conservative measures are permissible, particularly if diagnosis is too long deferred. Simple closure remains the treatment of choice according to most writers, with the exception of a few of the more radical surgeons, especially those on the Continent.

Surgical mortality from this condition is still high, owing in large part to delayed or mistaken diagnoses. For this reason one cannot emphasize too strongly the fundamental importance attaching to an early diagnosis of the condition by internists, who are for the most part concerned with the treatment of peptic ulcer.

A historically interesting summary of changes in age incidence and sex distribution of perforated peptic ulcer is presented by Jennings.[192] The author provides a rather unusual summary of changes that have apparently taken place in the past one hundred and fifty years in England, Germany, France, Scandinavia and the English-speaking countries. As good a statistical study as any is that presented by Odom and DeBakey,[193] who report an incidence of approximately 8 per cent of perforations in 2,600 patients with peptic ulcer admitted to the hospital wards during a ten year period. Reference to the majority of these articles is unnecessary for this review, as they are chiefly of surgical interest.

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191. Daniel, W. A., Jr., and Egan, S.: The Quantity of Blood Required to Produce a Tarry Stool, J. A. M. A. **113**:2232 (Dec. 16) 1939.

192. Jennings, D.: Perforated Peptic Ulcer: Changes in Age Incidence and Sex Distribution in Last One Hundred and Fifty Years, Lancet **1**:395, 1940.

193. Odom, C. B., and DeBakey, M.: Acute Perforated Gastric and Duodenal Ulcer, New Orleans M. & S. J. **92**:359, 1940.

Gjankovic [194] made an interesting observation on covered perforation of gastric and duodenal ulcer. The author reviews the literature on closed perforations of peptic ulcer and reveals that he encountered this condition in 10 per cent of his own operative cases. He admits that the prognosis of covered perforations is generally favorable and that spontaneous cure is possible but quite properly holds that surgical intervention is nearly always indicated, in spite of the possibility of such spontaneous protective measures.

The possibility of an associated hemorrhage with perforation is pointed out by several authors.[195] The important dangers and the treatment of peptic ulcers perforating into the pancreas are pointed out by Horsley.[196] Hadley [197] reports an unusual form of perforation of the stomach following antisyphilitic treatment of a gastric gumma, perforation being evidenced by roentgen examination. Another fortunately rare occurrence is that noted by Law,[198] who reports 2 cases of perforated jejunal ulcer subsequent to partial gastrectomy. Still another most unusual result of perforation of a duodenal ulcer is that reported by Gottlieb,[199] in which roentgen examination revealed the presence of gas in the biliary ducts. The preoperative diagnosis was duodenobiliary fistula, and operation and subsequent autopsy showed a duodenal ulcer of long standing with perforation clearly into the gallbladder.

Of diagnostic significance is the report of Feldman [200] on the effect of peptic ulcer activity on cholecystography. It has been repeatedly noted that apparently falsely positive cholecystograms are occasionally obtained in the presence of peptic ulcer without true disease of the gallbladder. Feldman reports the results of studies made in 115 cases of peptic ulcer. Ten per cent of the patients showed abnormal filling of the gallbladder, and more than 25 per cent appeared to have sluggish or noncontracting gallbladders. In 5 per cent of the 115 cases of ulcer, there were associated actual gallstones, an association which frequently makes accurate diagnosis difficult.

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194. Gjankovic, H.: Covered Perforation of Gastric and Duodenal Ulcer, Presse méd. **47**:1263, 1939.

195. Winters, W. L., and Egan, S.: Incidence of Hemorrhage Occurring with Perforation in Peptic Ulcer, J. A. M. A. **113**:2199 (Dec. 16) 1939. Meyer, H. W.: Perforation of the Gastrointestinal Tract, Ann. Surg. **112**:37, 1940.

196. Horsley, J. S.: Peptic Ulcers Perforating into the Pancreas, Ann. Surg. **110**:606, 1939.

197. Hadley, H. G.: Perforation of Stomach Due to Syphilis, Radiology **35**:86, 1940.

198. Law, W. A.: Perforated Jejunal Ulcer Following Partial Gastrectomy, Brit. M. J. **1**:844, 1940.

199. Gottlieb, C.: Visualization of Biliary Ducts by Means of Gas Following Spontaneous Duodenal Ulcer Rupture, Radiology **33**:470, 1939.

200. Feldman, M.: Effect of Peptic Ulcer in Cholecystography, Am. J. Roentgenol. **43**:58, 1940.

Small Intestine.—Reports on anatomic abnormalities of the duodenum are encountered as usual. Among them, the report by Feldman and Morrison [201] of 14 cases of inverted duodenum is of some interest. The significance of megaduodenum and "duodenal obstruction" is carefully discussed by Sturtevant.[202] He reviews thoroughly the various interpretations of this not uncommon condition, and perusal of his article reveals a sensible attitude toward the clinical significance and the therapeutic implications of this condition. He describes the characteristic roentgen picture leading to a diagnosis of obstruction but adds that even the presence of apparently typical roentgen criteria is not always conclusive. He states that true duodenal obstruction with dilatation is an entity, but a distinctly rare one. So much has been written on the subject that is based largely on rather loose clinical impressions that Sturtevant's article is of real value.

As a rule, it is unwise to attribute much clinical significance to accidental demonstrations of duodenal diverticula. Occasionally, however, they may be the cause of important clinical symptoms and may even lead to perforation, with serious results. The case reported by Boland [203] is worthy of note, particularly because of the rarity with which symptoms are encountered as a result of this uncommon abnormality. Two other rare instances of fatal abdominal emergencies secondary to perforation are reported by Roach [204] and by Ottenheimer and Gilman.[205] The case reported by Roach was one of fatal hematemesis caused by rupture of an abdominal aortic aneurysm into the third portion of the duodenum. Ottenheimer and Gilman report a case of traumatic rupture into the retroperitoneal portion of the duodenum following injury to the right side of the chest and the abdomen, an extremely rare condition. The few reports on primary malignant tumor of the duodenum that have appeared during the current year serve only to testify to the rarity of this disease.

The frequency of primary jejunal pathologic change was indicated in the statistical study of Browne and McHardy,[206] based on a statistical

201. Feldman, M., and Morrison, T. H.: Inverted Duodenum: Its Clinical Significance with Report of Fourteen Cases, Am. J. M. Sc. **20**:69, 1940.

202. Sturtevant, M.: Megaduodenum and Duodenal Obstruction: Criteria for Diagnosis, Radiology **33**:185, 1939.

203. Boland, F. K., Jr.: Acute Perforated Duodenal Diverticulum, Surgery **6**:65, 1939.

204. Roach, R. D.: Rare Cause of Fatal Hematemesis, Canad. M. A. J. **41**:173, 1939.

205. Ottenheimer, E. J., and Gilman, R. L.: Rupture of the Retroperitoneal Duodenum, New England J. Med. **222**:251, 1940.

206. Browne, D. C., and McHardy, G.: Primary Jejunal Pathology, J. A. M. A., to be published.

examination of nearly 8,000 autopsies. They encountered a single example each of traumatic regional enteritis and intussusception, 16 diverticula, 4 perforated ulcers and 11 neoplasms, of which 7 were benign and 4 malignant. These authors, together with Kiefer,[207] present excellent routine summaries of the clinical aspects of disorders of the jejunum and the small bowel and indicate the increasing interest in diagnosis of disease of a portion of the digestive tract previously avoided because of technical diagnostic difficulties. With the exception of disorders causing diarrhea, the symptoms of jejunal and ileal disease are fundamentally those of partial or complete obstruction, and too much attention cannot be paid to acquisition of a detailed history as to the occurrence of umbilical pain or peristaltic discomfort if an early diagnosis of jejunal and ileal lesions is to be expected.

An excellent résumé of the subject of intestinal obstruction due to intraluminal foreign bodies is that by Storck, Rothschild and Ochsner.[208] These authors review 875 cases of intestinal obstruction, exclusive of hernia, neoplasm and peritonitis. Obstruction in almost 6 per cent of these cases was due to foreign bodies, including gallstones, intestinal parasites, bezoars and a miscellaneous group of others. The clinical description included in the article is well worthy of study, and the large variety of foreign bodies mentioned seems to include almost all the possibilities.

Numerous articles on intestinal obstruction due to gallstones bear witness to the relative frequency of this complication of disease of the gallbladder. Snodgrass[209] adds nonabsorbable suture material to the list of foreign bodies capable of causing intestinal obstruction. His case is of interest because of the fact that material had been introduced into the abdomen twenty-four years previously.

It has long been known that bran may act as a real irritant to the gastrointestinal tract. A report by Fantus and Kopstein[210] indicates that its use may be associated with the production of intestinal obstruction in the presence of predisposing organic disease, and these authors properly advise against its use when intestinal ulceration, stenosis or adhesions are known to be present.

The number of reports on benign and malignant tumors of the small bowel is steadily growing and indicates a rapidly accumulating interest

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207. Kiefer, E. D.: Clinical Aspects of Chronic Disorders of the Small Intestine, J. A. M. A. **113**:1546 (Oct. 21) 1939.

208. Storck, A.; Rothschild, J. E., and Ochsner, A.: Intestinal Obstruction Due to Intraluminal Foreign Bodies, Ann. Surg. **109**:844, 1939.

209. Snodgrass, T. J.: Acute Intestinal Obstruction Caused by Nonabsorbable Suture Material, Surgery **6**:437, 1939.

210. Fantus, B., and Kopstein, G.: Does Bran Produce Intestinal Obstruction? Am. J. Digest. Dis. **7**:60, 1940.

and skill in dealing with disease of the small intestine. Among the best reports of malignant tumors of the small bowel are those by Medinger [211] and Cohn, and Landy and Richter.[212] Several articles record the finding of argentaffin tumors of the appendix and small bowel, the most complete report being that of Porter and Whelan.[213]

Reports, such as that by Pachman,[214] on such surgical rarities as enterogenous cysts are of interest merely for purposes of inclusion among potential causes of intestinal obstruction. Mere mention of innumerable other causes of intestinal obstruction will suffice, as individual reports add little that is new. Volvulus, obstruction secondary to the Baldy-Webster type of uterine suspension, torsion of the appendices epiploicae, intussusception following attacks of Henoch's purpura, Meckel's diverticulum, hyperplastic tuberculosis of the ileum, intestinal intussusception in infants and even extrinsic antenatal intestinal obstruction of the ileum all receive attention in a large series of articles, which are of interest merely for purposes of classification and surgical technic.

The entire question of intestinal obstruction, regardless of its underlying cause, is one that fundamentally involves surgical consideration. To internists, particularly those interested in gastroenterology, a diagnostic interest in the factors underlying the condition and a more complete understanding of the physiologic disturbances incident to it warrant inclusion of several articles that are primarily of surgical interest. Orr [215] records 2 cases of intestinal obstruction due to mechanical injury to the spine which was treated conservatively as paralytic ileus. The chief importance of the report is that it points out the necessity for establishing the cause of abdominal distention in relation to orthopedic conditions, among others. The discomfort of a distended abdomen beneath such a cast as might be applied to a patient suffering from spinal injury may be falsely interpreted as due to paralytic ileus, with delay in treatment and perhaps a fatal outcome. The occurrence of severe colicky pain in such a patient is indication for removal of the cast and further complete examination, to exclude actual obstruction.

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211. Medinger, F. G.: Malignant Tumors of Small Intestine: Study of Their Incidence and Diagnostic Characteristics, Surg., Gynec. & Obst. **69**:299, 1939.

212. Cohn, S.; Landy, J. A., and Richter, M.: Tumors of Small Intestine, Arch. Surg. **39**:647 (Oct.) 1939.

213. Porter, J. E., and Whelan, C. S.: Argentaffine Tumors: Report of Eighty-Four Cases, Three with Metastases, Am. J. Cancer **36**:343, 1939.

214. Pachman, D. J.: Enterogenous Intramural Cysts of Intestines, Am. J. Dis. Child. **58**:485 (Sept.) 1939.

215. Orr, T. G.: Paralytic Ileus and Intestinal Obstruction Complicating Skeletal Injuries, South. M. J. **32**:508, 1939.

Physiologic disturbances that may occur as a result of intestinal obstruction have been further studied by Gendel and Fine,[216] who record the result of experimental acute intestinal obstruction in dogs on blood plasma volume. They stress the importance of early progressive loss of blood plasma, which may reach 36 per cent within four to six hours, with a loss of plasma volume of as high as 55 per cent within twenty-four hours after production of the obstruction. Such a loss of plasma, which is equivalent to about 3 per cent of the body weight, is more than sufficient in itself to cause death and occurs particularly in cases in which strangulation is added to obstruction. Hematocrit readings, with direct evidence of the loss of plasma volume, are apparently more accurate as regards the patient's condition than are blood pressure readings. Administration of adequate quantities of plasma by the intravenous route is recommended by these authors, with sound reasons. They also show that the survival time of animals with obstruction and gaseous distention of the small intestine is inversely proportional to the level of the pressure in the lumen of the bowel. Such experimental data provide a reasonable basis for the necessary details of successful treatment.

Excellent summaries of actual results in treating acute mechanical obstruction of the small intestine are provided in the articles of McKittrick and Sarris,[217] Wangensteen [218] and Lupton,[219] all of whom stress the importance of decompression measures and replacement of fluids, electrolytes and plasma volume. Wangensteen emphasizes the importance of fluid loss in this condition in an estimate that approximately 7,000 cc. of fluid may enter the intestinal canal in the form of digestive juices. The indications for and limitations of decompression treatment by the use of the Miller-Abbott tube or the Wangensteen apparatus are well discussed by Rea,[220] who, with others, points out the dangers of failure to differentiate between paralytic ileus and acute mechanical obstruction. The use of lumbar block induced with procaine hydrochloride as a conservative method of treating acute ileus is recorded

216. Gendel, S., and Fine, J.: Effect of Acute Intestinal Obstruction on Blood and Plasma Volumes, Ann. Surg. **110**:25, 1939. Fine, J.; Rosenfeld, L., and Gendel, S.: Role of Nervous System in Acute Intestinal Obstruction: Experimental Investigation, ibid. **110**:411, 1939.

217. McKittrick, L. S., and Sarris, S. P.: Acute Mechanical Obstruction of Small Bowel: Its Diagnosis and Treatment, New England J. Med. **222**:611, 1940.

218. Wangensteen, O. H.: Experimental and Clinical Observations Relating to the Management of Acute Bowel Obstruction, Ann. Int. Med. **13**:987, 1939.

219. Lupton, C. H.: Intestinal Obstruction, Virginia M. Monthly **66**:610, 1939.

220. Rea, C. E.: Diagnosis and Treatment of Small Bowel Obstruction, Am. J. Surg. **46**:604, 1939.

by Novikov.[221] In more than half of a group of 140 patients admitted to the surgical clinic with acute intestinal obstruction procaine hydrochloride was injected into the right or the left iliac fossa, and in nearly two thirds of the cases procaine block alone resulted in diminution of pain, passage of flatus and a copious bowel movement. In a third of the patients so treated the maneuver relieved pain and caused some passage of flatus but no stool. Novikov advocates the method as offering a possibility of preoperative recognition and of effective treatment of functional ileus. He also believes it may prevent the transition of functional ileus into mechanical ileus. It is obvious, however, that again careful clinical judgment is necessary to differentiate between conditions definitely requiring immediate operation and those which will permit a reasonable delay. An unusual form of treatment of mechanical obstruction of the small intestine is that reported by Smith,[222] who presents the results of treatment by hyperthermia of 2 patients with obstruction of the small bowel secondary to gonorrheal adnexitis. Because of the danger of dehydration, chloride depletion and alkalosis inherent both in fever therapy and in intestinal obstruction, great caution is obviously necessary, but the report is of interest because of the specific nature of treatment for one of the known causes of intestinal obstruction.

Further evidence of the diagnostic value of roentgen studies after intubation of the small intestine in cases of partially obstructive lesions is presented by Boone,[223] who used the Miller-Abbott tube in this connection. Findings suggesting incomplete obstruction are permanent arrest in the passage of the balloon, unusual regurgitation of an injected barium mixture and persistent narrowing of the intestine distal to the shadow of the barium. With sufficient experience, one can undoubtedly localize and demonstrate pathologic processes in the bowel or its vicinity capable of causing intermittent or permanent narrowing.

Large Intestine.—As with conditions involving the small bowel, reports of congenital abnormalities of the colon are of interest largely because they call attention to already recognized but relatively uncommon conditions. A few articles concerned with megacolon will be mentioned. Tiffin, Chandler and Faber [224] report a case of megacolon in which the sigmoid flexure was of normal caliber but the entire colon above that

221. Novikov, G. M.: Procaine Hydrochloride Block in Acute Ileus, Vestnik khir. **58:** 506, 1939.

222. Smith, B. A., Jr.: Fever Therapy in Treatment of Mechanical Intestinal Obstruction Due to Pelvic Inflammatory Disease, Surgery **7:**61, 1940.

223. Boone, T. H.: Intubation of Small Intestine: Demonstration and Localization of Partially Obstructive Lesions, Lancet **1:**7, 1940.

224. Tiffin, M. E.; Chandler, L. R., and Faber, H. K.: Localized Abscess of the Ganglion Cells of the Myenteric Plexus in Congenital Megacolon, Am. J. Dis. Child. **59:** 1071 (May) 1940.

segment was abnormally dilated and hypertrophied. Administration of cholinergic drugs caused contraction of the bowel without propulsion of its contents, and sympathectomy did not influence the condition favorably. Histologic examination of the intestinal wall revealed that the cells of Auerbach's plexus were normal in number and appearance throughout the hypertrophied and dilated portion of the bowel but were greatly diminished or absent in the nondilated sigmoid flexure of the colon. The authors suggest that the condition appears to be closely related to that known to exist in the presence of cardiospasm or achalasia of the esophagus, in which absence of the peripheral neurons of the parasympathetic system has been observed. In this connection the work of Etzel, reviewed by Silva and de Paula,[225] is of interest, although in no way conclusive. Etzel believes that the destruction of Auerbach's plexus seen in cases of cardiospasm and megacolon is brought about by a deficiency in the vitamin B content of the diet. He found that practically all of his Italian patients with megacolon and megaesophagus came from a district where pellagra and dietary deficiencies are known to be of frequent occurrence. Law [226] describes the successful treatment of 6 children suffering from megacolon with acetylbetamethylcholine bromide. Two of these patients were able to discontinue the use of the drug after three and nine months, respectively. Such results, as well as those reported by Telford and Simmons [227] on successful treatment of megacolon in children in 7 cases and of megaesophagus in 1 case by the use of spinal anesthesia, still further contribute to the accumulating evidence of the fundamental role played by disturbances of the autonomic nervous system in these conditions.

To those interested in the diagnosis and treatment of congenital anomalies of the anus and rectum, attention may be directed to a fairly complete review of the subject by Crowell and Dulin.[228]

Diverticulosis of the colon, because of its frequent occurrence, continues to attract attention. An authoritative article by Buie [229] gives a complete description of colonic diverticula, including a description of prenatal and postnatal manifestations of the condition, incidence, anatomic situation, pathologic picture, relation of the disease to malignant

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225. Silva, G. S., and de Paula, E.: Chronic Vitamin B_1 Deficiency in the Etiology of Megoesophagus and Megacolon, editorial, Am. J. Digest. Dis. **7**:184, 1940.

226. Law, J. L.: The Treatment of Megacolon with Parasympathetic Drugs, J. A. M. A. **114**:2537 (June 29) 1940.

227. Telford, E. D., and Simmons, H. T.: Treatment of Gastrointestinal Achalasia by Spinal Anesthesia, Brit. M. J. **2**:1224, 1939.

228. Crowell, E. A., and Dulin, J. W.: Congenital Anomalies of the Anus and Rectum, Surgery **7**:529, 1940.

229. Buie, L. A.: Diverticula of the Colon, New England J. Med. **221**:593, 1939.

tumor of the colon and treatment. The author discusses rather fully the medical and the surgical treatment of this condition stating that the necessity for the latter arises in about 10 per cent of all cases. A particularly accurate and valuable description is given of the sigmoidoscopic findings associated with sigmoidal diverticulitis. He stresses the importance of suspecting the presence of malignant changes in patients with diverticulitis of the sigmoid flexure, with the necessity for complete and repeated studies to determine the benignity of the lesion. It might be added that there is no particular evidence that malignant disease is secondary to diverticulitis, the association being no more common than is to be noted in the average run of patients. Brown [230] stresses the frequency with which diverticulosis can be demonstrated, stating that it is present in about 5 per cent of persons 40 years old or older. The number of cases in which diverticulitis will sooner or later develop and in which operation will eventually be required is unpredictable. He stresses the rapidity with which symptoms requiring operation may develop in patients in whom symptomless diverticulosis has been present for a long time but agrees with other writers that medical treatment is entirely adequate in all but a small percentage of cases. The importance of acute perforative diverticulitis is brought out in his article and in that by Bearse,[231] and a rather unusual complication, pylephlebitis, the original cause of which is not frequently suspected, is reported by Pepper.[232]

Considerable attention is properly paid to the subject of polyps of the colon and rectum. A careful statistical and pathologic study of this condition is presented by Swinton and Warren [233] on the basis of observations in 156 patients and an analysis of more than 800 cases in which operation for carcinoma of the colon and rectum was done. They point out that the actual incidence of polypoid disease of the colon and rectum is not known but correctly believe that it is much more common than has been recognized. Certain important facts are discussed. Nearly three fourths of the polyps in this series could be visualized with a sigmoidoscope, a fact leaving little excuse for failure to examine instrumentally all patients with rectal bleeding. This particular point cannot be stressed too frequently or too earnestly. Another important observation in this series is that about one third of the patients had multiple

230. Brown, P. W.: The Treatment and Prognosis of Diverticulitis of the Colon, Am. J. Surg. **46**:162, 1939.

231. Bearse, C.: Acute Perforative Diverticulitis of the Colon in Young Persons, J. A. M. A. **113**:1720 (Nov. 4) 1939.

232. Pepper, O. H. P.: Diverticulitis of the Colon, Pennsylvania M. J. **42**: 1043, 1939.

233. Swinton, N. W., and Warren, S.: Polyps of the Colon and Rectum and Their Relation to Malignancy, J. A. M. A. **113**:1927 (Nov. 25) 1939.

polypi. Histologic examination of the material removed at operation showed all stages in the sequence of change from normal mucosa to adenocarcinoma. One seventh of over 800 patients with cancer of the colon and rectum presented almost certain evidence of malignant degeneration from previously benign polypoid tumors. The importance of these observations cannot be overestimated, although they are in no way new. That a diagnosis of polyps may be made on the basis of symptoms in children is evident from the report of Kennedy [234] on 42 instances of this condition in infants and children. The chief symptoms and signs directing attention to the disease were the presence of fresh blood in the stools and a mass protruding from the anus. An unusual example is the case report of a boy aged 7 years whose initial symptom, rectal bleeding, dated from the age of 3 months. An interesting complication of the successful surgical treatment in this particular case was the development of spontaneous bleeding on the twenty-fifth postoperative day, due to prothrombin deficiency.[235]

The importance of the relation between intestinal polyps and malignant disease is particularly well discussed by Coffey and Bargen.[236] The article is well worth reading because of its completeness. Among other interesting statistical facts is the statement that two thirds of a series of patients with multiple adenomatous polyps had carcinoma. Additional evidence of the recognized tendency to malignant degeneration and the familial incidence of carcinoma is to be found in articles by Lockhart-Mummery and Dukes [237] and McKenney.[238] The latter describes 4 siblings between the ages of 2 and 11 who had malignant degeneration from multiple polypi, and in the report by Lockhart-Mummery and Dukes a fairly complete study of the course of adenomatosis of the colon and rectum in ten families demonstrates convincingly the general familial character of the disease and its close relation to cancer, in a history that carried through several generations. A very important part of the article by Coffey and Bargen is the extremely careful description of polyposis arising as a complication of chronic ulcerative colitis. Of the polyps noted in the course of ulcerative colitis, 56 per cent were

234. Kennedy, R. L. J.: Polyps of the Colon and Rectum in Infants and Children, Proc. Staff Meet., Mayo Clin. **15**:108, 1940.

235. Dixon, C. F., and Gregg, R. O.: Management of Postoperative Intestinal Obstruction Complicated by Hemorrhage on the Basis of Prothrombin Deficiency, Minnesota Med. **23**:169, 1940.

236. Coffey, R. J., and Bargen, J. A.: Intestinal Polyps: Pathogenesis and Relation to Malignancy, Surg., Gynec. & Obst. **66**:136, 1939.

237. Lockhart-Mummery, J. P., and Dukes, C. E.: Familial Adenomatosis of Colon and Rectum: Its Relationship to Cancer, Lancet **2**:586, 1939.

238. McKenney, D. C.: Multiple Polyposis: Congenital, Heredofamilial, Malignant, Am. J. Surg. **46**:204, 1939.

pseudoadenomatous, 21 per cent were adenomatous and 21 per cent were carcinomatous. The incidence of cancer is obviously smaller than that noted in cases of intestinal polyps not associated with chronic inflammation but represents an important figure. The seriousness of the condition is indicated by the fact that the surgical mortality in this last group was 66 per cent, owing undoubtedly to the associated presence of ulcerative colitis. Of additional interest is the fact that with improved medical treatment of this condition the incidence of polyposis was reduced from approximately 16 per cent to 10 per cent, although the accuracy of roentgen diagnosis had increased tremendously.

The treatment of intestinal polyps is obviously surgical, but the enthusiasm evinced by certain authors for fulguration through a sigmoidoscope (Hedin [239] and Smith [240]) should not be taken to indicate that such a procedure is not without great risk except in the hands of very skilful operators.

Because of the appalling incidence of death from cancer of the rectum and colon, it is important to refer briefly to a number of articles directing attention to the diagnosis and treatment of this condition. The diagnosis should be made with much greater frequency by proper attention to easily elicited symptoms. Lahey [241] brings out this point very clearly in an analysis of a large group of cases. Histories taken in 300 proved cases of cancer, in which the tumors were equally divided in location between the right side of the colon, the left side of the colon and the rectum, showed that there was an alteration in intestinal function, abdominal cramps or abnormal stools in 97 per cent of the cases. The presence of abnormal stools was noted in 86 per cent of cases of cancer of the rectum and in nearly half of the cases of cancer of the left side of the colon but in less than 10 per cent of the cases in which there was involvement of the right side of the colon. Because of the almost certain influence of trauma, irritation and infection in predisposing to carcinomatous degeneration, the discovery of any of the aforementioned symptoms or of bleeding should lead to a most careful search for evidences of malignant disease. It is important to recognize that skilful and effective surgical measures are almost universally available in all important medical centers at present, and the denial of help until after obstructive symptoms have occurred, once a diagnosis has been established, is absolutely inexcusable, as has

239. Hedin, R. F.: Polypoid Disease of the Colon: Anatomical Measurements of the Colon Including Description of a Colonscope, Surgery **6**:909, 1939.

240. Smith, N. D.: The Diagnosis and Fulguration of Polyps in the Rectum and Sigmoid, Proc. Staff Meet., Mayo Clin. **15**:101, 1940.

241. Lahey, F. H.: Neoplasms of Cecum and Ascending Colon, Am. J. Surg. **46**:3, 1939.

been pointed out in numerous authoritative articles by well known surgeons.[242] One additional point of importance regarding the incidence of the condition, namely, the occurrence of cancer of the rectum and colon in young persons, is stressed by several writers,[243] all of whom report the occurrence of this condition in groups of persons well under the so-called cancer age.

Although radical surgical treatment of colonic and rectal malignant disease is the therapy of choice, it should not be forgotten that there is still a place for radiation therapy. A full description of the possibilities of radiologic treatment of cancer of the rectum is given by Berven,[244] who points out that preoperative roentgen treatment may be of real help in an attack on the undifferentiated types of cancer, particularly in cases of large disintegrating operable tumors. Patients in whom only an incomplete removal is possible or who refuse surgical procedures should be given the benefit of radiation therapy, as should all inoperable patients whose general health permits. Such treatment not infrequently provides an endurable existence for these patients for an appreciable period. The author believes that anorectal carcinoma of the cutaneous type should first be treated radiologically. He also points out that only during the last fifteen years has radiologic treatment been tested to any great extent and that with improved technic and instruments the benefits to be derived from this form of therapy still warrant considerable study. An article by Meland[245] is in accord with the foregoing comments, and in another report[246] on carcinoma of the anus the same author discusses the symptomatology of this condition and brings out one important point which usually escapes accurate interpretation. In several patients the presenting symptom was backache. This is worthy of attention, as it is not too infrequent that dis-

242. Allen, A. W., and Welch, C. E.: Malignant Diseases of Colon: Factors Influencing Operability, Morbidity and Mortality, Am. J. Surg. **46**:171, 1939. Stone, H. B., and McLanahan, S.: Carcinoma of the large Bowel: Surgical Aspects, J. A. M. A. **113**:2282 (Dec. 23) 1939. Ochsner, A., and DeBakey, M.: Operability, Morbidity and Mortality Factors in Carcinoma of the Colon, Am. J. Surg. **46**:103, 1939. Rankin, F. W., and Graham, A. S.: Cancer of the Rectum and Rectosigmoid: Diagnosis and Treatment, ibid. **46**:18, 1939.

243. Mayo, C. W., and Madding, G. F.: Carcinoma of Rectum and of Rectosigmoid in the Young, Arch. Surg. **40**:83 (Jan.) 1940. Rosser, C., and Kerr, J. G.: Cancer of the Rectum in Young Persons, J. A. M. A. **113**:1192 (Sept. 23) 1939. Rawls, W. B.: Carcinoma of the Colon Occurring in a Girl Thirteen Years Old, New York State J. Med. **40**:290, 1940.

244. Berven, E.: Radiologic Treatment of Cancer of Rectum, Acta radiol. **20**:373, 1939.

245. Meland, O. N.: What Can One Expect from Radiation in Carcinoma of Rectum and Anus? California & West. Med. **50**:403, 1939.

246. Meland, O. N.: Carcinoma of Anus, Am. J. Roentgenol. **43**:706, 1940.

cases at various levels of the gastrointestinal tract first give notice of their existence by symptoms strongly suggestive of disease of the vertebral column.

Individual instances of unusual colonic tumors, such as simple lymphomas and neurogenic fibromas, are reported but are of interest only as rare findings. One form of rectal tumor, however, is worthy of note, namely, that secondary to injection treatments for hemorrhoids. Jackman [247] reports 3 cases of submucosal tumor masses or rectal stricture subsequent to the use of oil base sclerosing preparations, which the author properly condemns. An unusual complication of cancer was that reported by Renander,[248] who points out that when perforation occurs in association with cancer of the proximal part of the colon it usually breaks into the duodenum, with development of a duodenal-colic fistula, while distal colonic cancer, especially that in the region of the splenic flexure, usually produces a gastrocolic fistula. The author reports 2 cases of cancer of the descending colon perforating posteriorly and laterally into the retroperitoneal space and suggesting the diagnosis of perinephritic abscess. Nonmalignant, subparietal rupture of the intestine due to muscular effort is an unusual example of colonic disease, but MacMillan [249] records 43 cases from the literature and 2 of his own. Although hernia was present in the majority of instances, in the author's own cases there was no herniation and no other injury of the abdominal wall, except that associated with muscular effort. The inclusion of a case report by Judd, Larsen and Tilden [250] of linitis plastica of the colon is warranted because of the diffuse involvement that was found. The entire descending colon showed evidence of this condition, and the term "malignant fibrosis" was suggested as less apt to mislead the surgeon with a false sense of security when microscopic examination reveals only fibrous tissue. A most unusual cause of massive rectal bleeding is found in 2 case reports by Fleet [251] and Ewell and Jackson.[252] Both describe the occurrence

247. Jackman, R. J.: The Differential Diagnosis, Pathologic Aspects and Treatment of Rectal Tumors of Chemical Origin, Proc. Staff Meet., Mayo Clin. **15**:188, 1940.

248. Renander, A.: Covered Perforations in Cancer of Colon, Acta radiol. **20**:257, 1939.

249. MacMillan, S. F.: Subparietal Rupture of the Intestine Due to Muscular Effort: Report of Two Cases, Ann. Surg. **111**:49, 1940.

250. Judd, J. R.; Larsen, N. P., and Tilden, I. L.: Linitis Plastica of Colon, Surgery **6**:278, 1939.

251. Fleet, G. A.: Misplaced Gastric Mucosa as a Cause of Massive Rectal Hemorrhage, Canad. M. A. J. **42**:216, 1940.

252. Ewell, G. H., and Jackson, R. H., Sr.: Aberrant Gastric Mucosa in the Rectum with Ulceration and Hemorrhage, Wisconsin M. J. **38**:641, 1939.

of profuse rectal bleeding secondary to aberrant gastric mucosa in the rectum in children. Previous reports of this condition are not available in the literature.

The possibility of fecal impaction as a cause of serious symptoms is too frequently overlooked by clinicians trained in the diagnosis of more formidable conditions. It is of importance, therefore, to allude to such articles as that by Benson and Bargen,[253] particularly because therapeutic measures, if carefully carried out, are almost always successful. Chronic constipation of years' duration in adults, the use of the barium sulfate meal and fecal masses formed by such substances as hygroscopic gums,[254] colloidal aluminum hydroxide[255] and the like, need but to be mentioned as possible causative factors in this condition. A careful report of a case of intestinal obstruction caused by colloidal aluminum hydroxide is of particular importance, as the patient to whom this preparation had been given died of intestinal obstruction. An obvious contributory factor was the concomitant administration of morphine over a period of days, in addition to the constant drip administration of the colloid. Practical therapeutic measures for treatment of fecal impaction are outlined by Benson and Bargen.

Because of the contribution of this anatomic finding to the production of intestinal disturbances, the description by Fine and Lawes[256] of the muscle fibers of the anal submucosa, with special reference to the "pecten band," is of interest. Four biopsy specimens obtained from patients with annular thickening of the anal submucosa ("pecten band") showed that this thickening was due to dense bands of muscle fibers, which by comparison with other biopsy specimens were thought to be palpable manifestations of well developed submucosal muscle distinct from the internal sphincter. The term "muscularis submucosae ani" is proposed for this submucosal muscle layer, which has apparently hitherto not been described and hypertrophy of which, due to various causes, leads to simple stenosis and symptoms of severe constipation.

The details of management necessary to successful surgical handling of the colon are outlined by various writers. The importance of maintaining a proper water and chemical balance is described accurately

253. Benson, K. W., and Bargen, J. A.: Fecal Impaction, Am. J. M. Sc. **198**: 541, 1939.

254. Wand, S. P.: Fecal Impaction Due to a Hygroscopic Gum Laxative, Am. J. Digest. Dis. **7**:297, 1940.

255. Havens, W. P.: Intestinal Obstruction Caused by Colloidal Aluminum Hydroxide, J. A. M. A. **113**:1564 (Oct. 21) 1939.

256. Fine, J., and Lawes, C. H. W.: On the Muscle Fibres of the Anal Submucosa with Special Reference to the Pecten Band, Brit. J. Surg. **27**:678, 1940.

and in detail by Orr.[257] Although the facts presented have been recognized for some time, constant reiteration of the importance of such measures is proper. Among disagreeable and sometimes dangerous symptoms following colonic operations are postoperative distention and urinary retention. Again, the conclusions involved are not new, but the article by Marden and Williamson[258] is of importance because these authors point out the therapeutic value of prostigmine methylsulfate in reducing the incidence of both complications. The number of cases in which this drug was employed was sufficiently large to warrant the clinical impression that its use was attended by gratifying results. The dangers of postoperative peritonitis incident to surgical treatment of the colon and rectum are so well known that use of sulfanilamide or its related compounds as a prophylactic measure was to have been expected. Although the number of patients so treated is too small to warrant any absolute conclusions, Garlock[259] indicates that use of this drug may be of value in reducing the dangers incident to this type of operation. Postoperative infection by gas bacilli represents a serious complication of colonic procedures. It is possible that sulfanilamide might be efficacious in dealing with such a serious complication, and the apparently successful therapeutic results obtained by Clute and Anglem[260] in 2 cases of polyvalent gas bacillus infection of the abdominal wall complicating cecostomy done for obstructing colonic cancer warrant the inclusion of such a measure when indicated.

Appendicitis.—The occurrence of approximately half a million deaths from appendicitis in the United States during the past thirty years, or a loss of approximately 20,000 lives annually, and a note that appendicitis rates tenth as a cause of death in Canada are statistical statements warranting continued reference to a condition which should be easily recognized and successfully treated.[261] That the high incidence of the disease is not limited to members of the white race is indicated

257. Orr, T. G.: Water and Chemical Balance in Surgery of the Colon, Am. J. Surg. **46**:70, 1939.

258. Marden, P. A., and Williamson, E. G.: Use of Prostigmine Methylsulphate in Prevention of Postoperative Intestinal Atony and Urinary Bladder Retention, Surg., Gynec. & Obst. **69**:61, 1939.

259. Garlock, J. H., and Seley, G. P.: Use of Sulfanilamide in Surgery of Colon and Rectum, Surgery **5**:787, 1939.

260. Clute, H. M., and Anglem, T. J.: Gas Infection of Abdominal Wall, New England J. Med. **221**:647, 1939.

261. Jackson, A. S.: Half a Million Deaths from Appendicitis, Illinois M. J. **76**:355, 1939. Ochsner, A., and Murray, S.: Appendicitis, Am. J. Surg. **46**:566, 1939. Munroe, A. R.; Hoare, E. S., and Cristall, E.: Mortality of Appendicitis, Canad. M. A. J. **40**:463, 1939.

by reports from the Philippines [262] and from the Netherland East Indies.[263] In the latter group, however, Fossen and Baeke record an interesting fact that they have apparently demonstrated in Batavia. A study of entries to the hospital due to acute appendicitis reveals that the incidence of this condition among the Europeans was definitely higher than among the Chinese or the native Netherland East Indians. However, the authors point out that histologic studies on the appendixes of the different racial stocks revealed that signs of inflammation occurred in a large percentage of appendixes incidentally removed in natives and Chinese. In fact, the morbidity of the condition among the latter was even higher than among the Europeans, but it seems that the clinical manifestations are much less frequent than among Europeans. It is also important to recall the fact, recited by Parsons,[264] that statistics show that appendicitis in 50 per cent of all cases occurs within the first twenty years of life. In 2.5 per cent of this number it occurs between the ages of 1 and 5 years, and in 6 per cent, between the ages of 6 and 12 years. The mortality in children under 5 years of age averages from 15 to 25 per cent. Although statistical evidence on the subject is difficult to obtain, the article by Perry and Keeler [265] suggests that some family pedigrees supply convincing evidence that peculiarities or anomalies of the appendix are inherited as simple dominant unit characters. The authors conclude from the literature and from their studies that there are a number of hereditary factors predisposing to appendicitis. In the family described the upper section of the pedigree includes an incidence of 6.5 per cent, whereas in the lower section more than five times as many cases are encountered. The pedigree presented by the authors is by far the most extensive yet placed on record.

The actual causation of appendicitis must involve several factors, but examination of the literature makes it apparent that in the majority of cases appendicitis is the result of a form of closed loop obstruction, most frequently due to the presence of an impacted fecalith, pinworms or some other agent of obstruction. An ingenious set of observations by Wangensteen and Dennis [266] supports this thesis. The authors took occasion to note the behavior of a ligation of the appendix in 22

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262. Estrada, J. J., and Meñez, S. C.: 20,000 Cases of Appendicitis, J. Philippine Islands M. A. **19**:653, 1939.

263. Fossen, A., and Baeke, H. E.: Frequency of Acute Appendicitis in Netherland East Indies, Geneesk. tijdschr. v. Nederl.-Indië **79**:2857, 1939.

264. Parsons, E. O.: Appendicitis in Children, J. Kansas M. Soc. **41**:51, 1940.

265. Perry, T., Jr., and Keeler, C. E.: Appendicitis in Single Family Pedigree, Am. J. Surg. **46**:259, 1939.

266. Wangensteen, O. H., and Dennis, C.: Experimental Proof of Obstructive Origin of Appendicitis in Man, Ann. Surg. **110**:629, 1939.

patients, in whom it was possible to exteriorize the greater portion of the right half of the colon during operation for local cancer. Intraluminal pressures due to secretion of the thus ligated appendix were measured, and a pathologic picture identical to that of appendicitis was observed. In those instances in which there was no evidence of secretory pressure, luminal obstruction did not reproduce the picture of appendicitis. On the other hand, in those instances in which high secretory pressures were noted there was factual proof of such spontaneous appendicitis. The authors conclude that it appears likely that the chief inciting agency in bringing about appendicitis in man is obstruction of an appendix in which the mucosa (not atrophic) possesses normal secretory capacity.

The existence of appendicitis due to trauma is carefully discussed by Connell,[367] who was able to obtain data in response to a questionnaire on the incidence of such a condition in only a few cases. Eighty-one surgeons operating in over 72,000 cases of acute appendicitis answered the questionnaire, but there was no uniformity of opinion. Answers to questions submitted to thirty hospitals reporting nearly 50,000 cases gave a history of trauma in only 11 cases, and the author is wisely skeptical of the theory that trauma, by forcing fecal contents into the appendix, is a cause of acute appendicitis. Pease [268] also discusses the subject and asserts that traumatic appendicitis is a definite clinical entity that should be recognized not only by the physician but by the courts in questions of litigation and compensation. His study, however, is not nearly so complete and convincing as the preceding one.

The factors contributing to the mortality from acute appendicitis are well known and continue to be discussed in various articles. The duration of the disease before surgical intervention, the use of cathartics and the presence of diabetes certainly constitute the most important causes leading to an increased mortality. The well recognized increase in mortality from this condition among elderly persons is discussed carefully by Stalker.[269] He points out the unfortunate fact that in spite of mild initial symptoms of cramplike pain and tenderness in the right lower abdominal quadrant combined with leukocytosis, which should properly lead to a correct diagnosis, progressive gangrene and rupture of the appendix during the succeeding forty-eight hours usually produce no acute symptoms, and the patient more frequently than not seeks no medical advice, at times remaining ambulatory until an abscess develops. For the more complicated conditions, associated with local

267. Connell, J. E. A.: Trauma and Appendicitis, Surgery **7**:47, 1940.

268. Pease, G. N.: Traumatic Appendicitis, Journal-Lancet **59**:539, 1939.

269. Stalker, L. K.: Appendicitis Among Individuals More Than Sixty Years of Age, Surg., Gynec. & Obst. **71**:54, 1940.

or generalized peritonitis, the value of such procedures as duodenal decompression, transfusion, intelligent use of morphine and fluids, employment of sulfanilamide or related compounds and use of various serums or other measures to produce satisfactory local immune reactions is discussed in a large number of articles by different authors. These are chiefly of surgical interest, and a more complete treatment of this important subject may be found in a separate review.[270]

A recital of the diagnostic uncertainties of "chronic appendicitis" is important because of the surgical implications. Alvarez [271] is to be congratulated on his presentation of this controversial subject. His article properly condemns the poor surgical judgment frequently evinced in many cases in which a condition is so labeled and cites some figures and facts that are not given but are of interest. One of the causes for the mistaken diagnosis of appendicitis is the syndrome of abdominal pain secondary to mesenteric adenopathies. Again, this subject is not new but has been sanely discussed by Parini.[272]

Bacterial and Parasitic Diseases of the Intestine.—The difficulties inherent in any bacteriologic study of the intestinal tract are well known, but results of intubation studies of the human small intestine obtained by Nichols and Glenn [273] are of some interest. These authors studied the bacterial flora of the human throat, stomach and ileum, employing for the first time a Miller-Abbott tube to secure ileac specimens. Both aerobic and anaerobic cultures demonstrated a marked similarity in the organisms from the three areas, with variations in frequency rather than in type of bacteria noted. A further approach to the same subject is made by Porter and Rettger,[274] who observed the influence of diet and the distribution of bacteria in the stomach, small intestine and cecum of the white rat. Contrary to much prevailing opinion, the stomach and small intestine of the albino rat under most dietary conditions contained appreciable numbers of viable bacteria.

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270. Jones, C. M.: Report on Medical Progress: Gastroenterology, New England J. Med. **222**:634, 1940.

271. Alvarez, W. C.: When Should One Operate for Chronic Appendicitis? Study of Three Hundred and Eighty-Five Cases, J. A. M. A. **114**:1301 (April 6) 1940.

272. Parini, A.: Abdominal Syndromes from Adenopathies of Mesentery, Arch. ital. di chir. **56**:314, 1939.

273. Nichols, A. C., and Glenn, P. M.: Intubation Studies of the Human Small Intestine: XVI. The Bacterial Flora of the Ileum Compared with That of the Throat and Stomach in Normal Subjects, J. Lab. & Clin. Med. **25**:388, 1940.

274. Porter, J. R., and Rettger, L. F.: Influence of Diet on the Distribution of Bacteria in the Stomach, Small Intestine and Cecum of White Rats, J. Infect. Dis. **66**:104, 1940.

The so-called normal bacterial flora can be altered throughout the digestive tract by certain foods or by starvation, but it is fairly stable irrespective of the diet. Once the flora has been changed, it can be transformed back to normal by administration of appropriate diets. In a few instances, there appeared to be a relation between the hydrogen ion concentration of the contents of the lower part of the ileum and the cecum, the bacteriologic picture and the diets employed.

Carbohydrate intolerance in cases of intestinal fermentation or fermentative diarrhea is undoubtedly associated with abnormal intestinal flora. Serious consideration is given to this condition by Holmgren [275] in an article which is of interest because he reviews many of the bacteriologic studies that have been made and indicates the high incidence of hypochlorhydria or achlorhydria. The symptoms are thoroughly described, but one cannot entirely agree with the author's enthusiasm in attempting to dignify the syndrome by considering it true enterocolitis. The value of a low carbohydrate diet for this condition and possibly for true colitis is discussed by Voegtlin.[276] Both he and Oppenheimer [277] indicate the frequent increase in flatulence due to fermentation or colonic irritability when cathartics or other "cleansing" agents are utilized, and the latter gives a rather admirable discussion on the entire subject of "gas in the bowels" and its clinical significance in conditions not associated with increased fermentation.

Specific infection of the intestinal tract by a tubercle bacillus is noted with decreasing frequency by the average practitioner of medicine, as patients suffering from such conditions tend more and more to become segregated in institutions for the treatment of tuberculosis. The accurate diagnosis of intestinal tuberculosis, however, is still extremely important, although no exact specific procedures are as yet available. Careful roentgen study, sigmoidoscopy and stool examinations, which may exclude other conditions and present suggestive evidence of tuberculous involvement, must be carried out in numerous cases of diarrhea before a final diagnosis is possible. Roentgen diagnostic criteria have already become fairly widely recognized since the extensive studies of Brown and others. Valuable clinical and pathologic studies of this condition are those by Hardt and his collaborators,[278] Bellinger,[279]

275. Holmgren, I.: Fermentative Dyspepsia and Fermentative Enterocolitis, Acta med. Scandinav. **99**:476, 1939.

276. Voegtlin, W. L.: Low Carbohydrate Diet in Functional Disorders of the Large Bowel, Northwest Med. **38**:252, 1939.

277. Oppenheimer, A.: Gas in the Bowels: Observations and Experiments in Man, Surg., Gynec. & Obst. **70**:105, 1940.

278. Hardt, L. L.; Weissman, M.; Cook, C. E., and Martin, C. L.: Tuberculous Enterocolitis: Diagnostic Data, Illinois M. J. **76**:229, 1939.

279. Bellinger, G. C.: Diagnosis and Treatment of Intestinal Tuberculosis, Northwest Med. **38**:344, 1939.

Freilich and his co-authors [280] and Cullen.[281] That tuberculous enterocolitis can exist in the absence of active pulmonary involvement is still not sufficiently well recognized, and the report of Bockus, Tumen and Kornblum [282] adds an excellent discussion of this particular clinical procedure. Because of the high incidence of viable and virulent tubercle bacilli in the lower part of the sigmoid flexure of the colon and the rectum in cases of pulmonary tuberculosis, with the consequent probability of tissue contamination, Martin, Lansford and Sweany [283] contribute the important observation that stool cultures and animal inoculation are of little value in establishing the tubercle bacillus as a cause of anal fistula or abscess, in contrast to the real value of histopathologic examination of the tissues.

Continued observations on the value of intramuscular injections of calcium gluconate in the treatment of intestinal tuberculosis are found in an article by Pisani,[284] although the author recognizes that extensive postmortem observations are still needed before definite conclusions as to the value of this particular form of treatment can be drawn. He also admits the difficulty of treatment of intestinal tuberculosis unless the pulmonary lesions that are almost invariably present are under complete control.

The differential diagnosis of the diarrheas involves consideration of so many etiologic factors that a complete survey of the literature on this subject is not permissible in this review. A good summary of the situation is that by Manson,[285] who in a rather textbook-like fashion presents a complete summary of all the possible causes of such a symptom. The article includes a discussion not only of bacterial and parasitic agents but of such constitutional conditions as pernicious anemia, endocrine disturbances and avitaminosis.

Numerous reports on infantile diarrheas are encountered. Snyder [286] made an interesting investigation of fecal flora in 22 normal infants under

280. Freilich, E. B.; Coe, G. C., and Wien, N. A.: Gastrointestinal Tuberculosis: Correlation of Clinical Diagnoses and Autopsy Findings in Eighty Cases, with Review of Literature, Rev. Gastroenterol. **6**:483, 1939.

281. Cullen, J. H.: Intestinal Tuberculosis: Clinical Pathological Study, Quart. Bull., Sea View Hosp. **5**:143, 1940.

282. Bockus, H. L.; Tumen, H., and Kornblum, K.: Diffuse Primary Tuberculous Enterocolitis, Ann. Int. Med. **13**:1461, 1940.

283. Martin, C. L.; Lansford, W. I., and Sweany, H. C.: Etiology of Tuberculous Anal Abscess and Fistula, Am. J. Digest. Dis. **7**:36, 1940.

284. Pisani, V. V.: Intestinal Tuberculosis and Calcium Gluconate, Am. Rev. Tuberc. **40**:571, 1939.

285. Manson, T. J.: Differential Diagnosis of the Diarrheas, J. Tennessee M. A. **32**:276, 1939.

286. Snyder, M. L.: Normal Fecal Flora of Infants Between Two Weeks and One Year of Age: I. Serial Studies, J. Infect. Dis. **66**:1, 1940.

1 year of age. Carey [287] provides a good clinical discussion of the gastrointestinal symptoms associated with infections of the respiratory tract in children and several good descriptions [288] of epidemics of infantile diarrhea in different parts of the world are available. An imposing number of carefully authenticated, bacteriologically proved accounts of epidemics in children and adults due to Shiga, Flexner, Sonne, "Newcastle" and unrelated dysentery bacilli, the various members of the Salmonella group, Gärtner bacillus (Bacterium enteritidis), staphylococcus and nonhemolytic short chain streptococcus are to be found.[289] Their appearance in the current literature not only is indicative of the multiple factors present as possible causative agents in epidemic diarrheas but attests the increasing appreciation of their importance. This is particularly true when one notes the widespread geographic distribution of these various reports.

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287. Carey, J. F.: Gastrointestinal Symptoms of Respiratory Infections in Children, Illinois M. J. **76**:325, 1939.

288. Castello, J. P., and Lind, H. E.: Epidemic of Nursery Diarrhea, South. M. J. **32**:620, 1939. Barrera, B.: The Pathology and Bacteriology of Ileocolitis in Children, J. Philippine Islands M. A. **19**:345, 1939. Smellie, J. M.: Infantile Diarrhea, Lancet **1**:1026, 1939.

289. Cooper, M. L.; Furcolow, M. L.; Mitchell, A. G., and Cullen, G. E.: Relation of Dysentery to Acute Diarrhea of Infants and Children, J. Pediat. **15**:172, 1939. Hardy, A. V.; Watt, J.; Kolodny, M. H., and De Capito, T.: Studies of the Acute Diarrheal Diseases: III. Infections Due to the "Newcastle Dysentery Bacillus," Am. J. Pub. Health **30**:53, 1940. Woolpert, O. C.; Marsh, H. F., and Yaw, O. K.: Bacillary Dysentery Resulting from an Accidental Laboratory Infection, J. A. M. A. **113**:753 (Aug. 23) 1939. Tulloch, W. J.: Observations Concerning Bacillary Food Infection in Dundee During 1923-1938, J. Hyg. **39**:324, 1939. Beck, A., and Buckle, D. F.: Bacteriological Findings in an Epidemic of Sonné Dysentery, ibid. **39**:311, 1939. Block, N. B., and Ferguson, W.: An Outbreak of Shiga Dysentery in Michigan in 1938, Am. J. Pub. Health **30**:43, 1940. Godfrey, E. J., and Pond, M. A.: A Hospital Epidemic of Flexner Dysentery Caused by Contaminated Ice, J. A. M. A. **114**:115 (March 30) 1940. Massey, L. D., and Louckes, H.: A Study of Bacillary Dysentery, J. Arkansas M. Soc. **36**:180, 1940. Guthrie, K. J., and Montgomery, G. L.: Infections with Bacterium Enteritides in Infancy with Triad of Enteritis, Cholecystitis and Meningitis, J. Path. & Bact. **49**:393, 1939. Brown, E. G.; Combs, G. R., and Wright, E.: Food-Borne Infection with Salmonella Aertrycke, J. A. M. A. **114**:642 (Feb. 24) 1940. Birge, E. A.: Similarity of Chronic Infections with Salmonella Typhimurium and Tuberculosis in Guinea Pigs, Am. J. Pub. Health **29**:1125, 1939. Schiff, F., and Strauss, L.: Occurrence of Several Unusual Types of Salmonella in Human Infections, J. Infect. Dis. **65**:160, 1939. Abele, C. A., and Damon, S. R.: Outbreak of Gastro-Enteritis Caused by Milk-Borne Staphylococci Producing an Enterotoxin, J. M. A. Alabama **9**:1, 1939. Slocum, G. G., and Linden, B. A.: Food Poisoning Due to Staphylococcus, with Special Reference to Staphylococcus Agglutination by Normal Horse Serum, Am. J. Pub. Health **29**:1344, 1939. Minor, L. W.: An Outbreak of Gastro-Enteritis in Middletown in 1938, J. Connecticut M. Soc. **3**:615, 1939.

As was to be expected, nearly all of these epidemics appear to have been spread by food handlers, and they illustrate the existing need for further education of the public and of physicians in public health measures directed toward prevention of these communicable diseases. They also indicate clearly the obligation, as well as the opportunity, for the practicing physician to attempt through hospital or public health laboratories a search for the causative agents of many of the more important forms of infectious diarrhea.

The importance of vitamin deficiency as a factor conducive to the development of bacillary dysentery is suggested by the studies of Janota and Dack.[290] These authors demonstrated that monkeys which were known to be carriers of Flexner organisms generally showed clinical manifestations of bacillary dysentery when placed on a diet deficient in vitamin "M."

Animal experimentation on the value of protective vaccines against various organisms of the dysentery bacillus group and immunologic studies on human subjects are reported by Prigge.[291] Encouraging results in animals were definitely obtained, and serologic tests on human subjects disclosed the appearance of specific protective substances in the blood. A final estimate of the efficacy of these endotoxin-toxin-antiserum vaccines (ETA) on the basis of clinical experience is still to be made, but it is already known that polyvalent Flexner bacillus vaccine can be used with some success as a prophylactic measure. Prigge points out, however, that if vaccine treatment against dysentery is to be put into practice, the polyvalent mixed vaccines must be employed. These contain, in addition to the antigens of the Shiga-Kruse group, those of the more important "toxin deficient" dysentery bacilli and of the Flexner and Kruse-Sonne groups.

Two articles[292] on the value of transfused blood taken from artificially immunized donors in the treatment of chronic bacillary dysentery are also of some interest, although the number of patients treated was insufficient for any adequate conclusions as to the efficacy of such a maneuver.

It was inevitable that the effects of sulfanilamide on bacillary dysentery should be given a clinical trial. Jones and Abse,[293] after

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290. Janota, M., and Dack, G. M.: Bacillary Dysentery Developing in Monkeys on "Vitamin M" Deficient Diet, J. Infect. Dis. **65**:219, 1939.

291. Prigge, R.: Active Protective Vaccination Against Bacillary Dysentery, Klin. Wchnschr. **19**:337, 1940.

292. Felson, J. C.: Clinical Notes on the Use of Immunized Donors in Chronic Bacillary Dysentery, Am. J. Digest. Dis. **7**:81, 1940. Turell, R.: Transfusion of Blood from Artificially Immunized Donor in the Treatment of Chronic Bacillary Dysentery, J. Lab. & Clin. Med. **25**:706, 1940.

293. Jones, E., and Abse, D. W.: Sulfanilamide Therapy in Bacillary Dysentery, J. Ment. Sc. **85**:1259, 1939.

laboratory experiments, gave sulfanilamide to 21 patients suffering from bacillary dysentery (Flexner W). Uniformly favorable results were noted, and it is to be hoped that further observations, including studies on the effect of the drug on dysentery carriers, will be made. The use of pectin, pectin agar and metal pectinates in the treatment of infectious diarrheas continues to attract attention, and articles [294] from the laboratories and clinics continue to appear, testifying to the therapeutic value of these preparations in cases of bacillary dysentery and other forms of bacterial invasion of the intestinal tract. Perusal of the literature would seem to warrant the conclusion that pectin-containing substances, particularly when combined with metallic ions, such as nickel, possess definite bacteriostatic and bactericidal properties, especially in the more acute infectious diarrheas. Whether these preparations offer more than palliative relief of the more serious or chronic forms of diarrhea due to bacterial invasion of the intestine is open to real question, and it must also be remembered that from many of the acute forms of infectious diarrhea the patients recover rapidly with almost any simple form of therapy. Further carefully controlled clinical studies on the use of such preparations are needed before any final conclusion can be reached as to their efficacy.

While considering infections of the intestinal tract, it is important to call attention to a further observation by Kramer and his associates,[295] who continue their search to recover the virus of poliomyelitis from the intestinal contents. During an epidemic of poliomyelitis in a children's home, the authors isolated the virus from the stools of 3 of 12 healthy children who had been in contact with patients suffering from the disease and from 2 of 3 other children who had noticeable fever but no clinically diagnostic paralysis. Thus, including the 5 with clinical infections, 10 of the 20 children who were in contact harbored the poliomyelitis

294. Manville, J. A., and Sullivan, N. P.: Relationship of the Diet to the Self-Regulatory Defense Mechanism: III. Organic Acids and Pectin, Am. J. Digest. Dis. **7**:111, 1940; The Bactericidal Action of Metallic Ions in Broth Containing Dehydrated Apple, ibid. **7**:106, 1940. Cruz, F. Z.: Local Observation on the Use of Fresh Apple in Gastro-Enteritis, J. Philippine Islands M. A. **19**:611, 1939. Kutscher, G. W., Jr.: The Rôle of Pectin in Diarrhea, North Carolina M. J. **1**:107, 1940. Kutscher, G. W., Jr., and Blumberg, A.: The Use of Pectin Agar Mixtures in Diarrheas, Am. J. Digest. Dis. **6**:717, 1939. Winters, M.; Tompkins, C. A., and Crook, G. W.: Pectin Agar Diets in Treatment of Bacillary Dysentery of Infants and Children, J. Pediat. **14**:788, 1939. Myers, P. B., and Rouse, A. H.: Pectinates with Special Reference to Nickel Pectinate and Their Therapeutic Value, Am. J. Digest. Dis. **7**:39, 1940.

295. Kramer, S. D.; Gilliam, A. G., and Molner, J. G.: Recovery of Virus of Poliomyelitis from Stools of Healthy Contacts in Institutional Outbreak, Pub. Health Rep. **54**:1914, 1939.

virus at some time, and the virus was also found in the stool of the day nurse in charge. From the public health point of view, the importance of these findings is obvious. Also of public health interest is the note by Tucker and Swanson [296] of a small outbreak of botulism due to botulinus toxin subsequently demonstrated to be present in home-canned vegetables.

A constantly growing recognition of the important role of gastrointestinal parasites in man as the cause of displeasing or dangerous symptoms is evident in the gastroenterologic literature of recent years. Detailed reports [297] on human intestinal parasites from such widely separated areas as Alabama, the northeastern seaboard states, Indiana, Colorado and Saskatchewan indicate the importance of and interest in such conditions. Particular interest centers on the infestation of the digestive tract with Endamoeba histolytica, but to those physicians not entirely familiar with methods of search for other parasites, such as Ascaris, Taenia nana, Trichiuris trichiura and others, careful perusal of these articles will be of benefit.

The more serious aspects of amebic infestation are well recognized. The clinical significance of the carrier still, however, is an important consideration, and a study by Howard [298] on 22 carriers of E. histolytica is of some interest as regards the effect of therapy on minor symptoms commonly attributable to this condition. Only one fourth of his patients were freed from abdominal symptoms by specific antiamebic treatment. Such a result indicates the wisdom of searching for amebiasis in patients with vague gastrointestinal complaints, but too striking clinical improvement should not be expected from the amebicidal treatment of carriers. This conclusion is not in keeping with those expressed by many writers who are more enthusiastic than critical concerning the therapeutic results of specific medication. A somewhat similar clinical study by Sapero [299] of cases of nondysenteric intestinal amebiasis indicates the incidence of minor digestive symptoms in amebic carriers, as contrasted with the rela-

296. Tucker, C. B., and Swanson, H.: Outbreak of Botulism in Tennessee Due to Type B Clostridium Botulinum, Pub. Health Rep. **54**:1556, 1939.

297. Smith, W. H. Y.; Gill, D. G., and McAlpine, J. G.: Intestinal Parasite Survey in Alabama, South. M. J. **32**:1094, 1939. Connell, F. H., and French, H. T.: The Incidence and Results of Treatment of Subclinical Amebiasis, J. A. M. A. **113**:649 (Aug. 19) 1939. Kmecza, J. M.: The Incidence of Human Intestinal Parasite Infections Among Patients in a State Institution of Indiana, Am. J. Trop. Med. **19**:515, 1939. Chisholm, A. J.: Amebiasis, Rocky Mountain M. J. **36**:870, 1939. Miller, M. J.: Intestinal Protozoa of Man in Saskatchewan, Canad. M. A. J. **41**:120, 1939.

298. Howard, J. T.: The Clinical Significance of the Carrier State in Amebiasis, Am. J. Digest. Dis. **6**:506, 1939.

299. Sapero, J. J.: Clinical Studies in Nondysenteric Intestinal Amebiasis, Am. J. Trop. Med. **19**:497, 1939.

tive freedom from complaints of patients harboring many other parasites. Again, hospitalization and antiamebic treatment were beneficial only in a rather carefully chosen group of patients harboring this infestation without dysenteric symptoms. An unusual opportunity for a study of the food handler as a transmitter of amebiasis is that recorded by Schoenleber.[300] He reports observations made in the island of Aruba, to which were transported 1,500 Americans recruited from localities in the United States where the average amebic infestation rate is not more than 10 per cent. These persons lived for years in the island without prophylactic measures against dissemination of amebic infestation by carriers. The group lived under conditions which precluded the possibility of acquiring it from water, flies, sewage or soil contamination of food. Examinations of the stool after some period of residence showed an annual infestation rate of 25 per cent and an amebic colitis rate of 36 per thousand. Examinations of the stools of food handlers showed that one third were carriers. As a result of active measures for control of dissemination of the infestation only by food handlers, the infection rate was reduced 50 per cent after one year and 92 per cent after three years of such activities, a valuable and conclusive experience in the efficacy of specific public health measures.

For a rather complete review of all the accepted methods of antiamebic therapy, the reader is referred to recent articles by Shattuck [301] and by Mateer and others,[302] who discuss in detail the utilization of emetine, carbarsone, chiniofon and vioform, with their various indications and contraindications. A report from Batavia by van Wesel [303] recites his experiences with the use of arsphenamine preparations in the treatment of amebic dysentery and amebic hepatitis refractory to other drugs. The results reported are not entirely conclusive but without question warrant serious consideration of such a procedure for otherwise intractable conditions. Amebic granuloma is most frequently located in the cecum and in the flexures of the colon. It occasionally occurs in the rectum, however, and may readily be mistaken for a malignant growth, as the associated symptoms and proctoscopic appearance are not dissimilar to those of carcinoma; indeed, the two conditions may be combined in a single lesion. Biopsy of such lesions is of the utmost impor-

300. Schoenleber, A. W.: The Food Handler as a Transmitter of Amebiasis, Am. J. Trop. Med. **20**:99, 1940.

301. Shattuck, G. C.: Treatment of Amebiasis, M. Clin. North America **23**: 1269, 1939.

302. Mateer, J. G.; Baltz, J. I.; Marion, D. E., and Hollands, R. A.: The Treatment of Amebiasis by a Combined Method: Statistical End Results, Am. J. Digest. Dis. **7**:154, 1940.

303. van Wesel, R.: Treatment of Amebic Dysentery and Amebic Hepatitis with Arsphenamine, Geneesk. tijdschr. v. Nederl.-Indië **79**:825, 1939.

tance, and 3 such cases are reported by Hummel [304] and by Donald and Brown.[305] The identity of the lesion was established by microscopic examination of scrapings obtained through a sigmoidoscope, and specific therapy 5,7-diiodo-8-hydroxyquinoline (diodoquin) produced entirely satisfactory results. The surgical aspect of amebiasis is completely summarized by Ochsner and DeBakey,[306] who present an excellent review of the subject in all its details. To those unfamiliar with these more serious aspects of infection by this particular parasite, the article is worthy of very careful reading. On the basis of Craig's estimate that between 6,000,000 and 12,000,000 persons in the United States are infected with E. histolytica and the known fact that hepatic complications occur in approximately 4 to 5 per cent of persons with amebic dysentery, it can be readily seen that a knowledge of its significance, diagnosis and treatment is of real clinical importance.

The important diagnostic aid to be obtained by careful roentgen examination in cases of colonic disease of obscure origin is still not well recognized by many roentgenologists and internists. Various abnormalities of the colon may be recognized in the subchronic and chronic forms of amebic dysentery, the most characteristic finding being segmental distribution of narrowed or atonic bowel. These findings are carefully reviewed in an article by Meves,[307] of Leipzig, Germany, who examined a large group of persons who had previously contracted amebic dysentery and who had persistent symptoms in spite of previous therapy.

Few reports of disease due to Balantidium coli in this country have appeared prior to one by Young,[308] who adds a record of 9 cases from South Carolina and Tennessee to the 32 cases already to be found in the literature. Swine are generally thought to be the source of most such infections in man, but epidemiologic studies indicate that in the cases under discussion the infections were contracted from human sources. The infected patients had chronic diarrhea and occasional acute dysenteric attacks, but it is not clear that the symptoms were entirely due to infestation by Balantidia, as 3 other parasites were also found as a result of frequent examinations of the stool. Carbarsone therapy resulted in the disappearance of Balantidia from the stools in 2 patients, but oil of chenopodium given orally appeared to be ineffective.

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304. Hummel, H. G.: Amebic Granuloma of the Rectum and Balantidiasis in the Same Patient, Am. J. Digest. Dis. **7**:178, 1940.

305. Donald, C. J., Jr., and Brown, P. W.: Amebic Granuloma Simulating Carcinoma of the Rectum, Proc. Staff Meet., Mayo Clin. **15**:331, 1940.

306. Ochsner, A., and DeBakey, M.: Surgery of Amebiasis, New Orleans M. & S. J. **91**:670, 1939.

307. Meves, F.: Roentgenographic Observations in Chronic Amebic Dysentery, Fortschr. a. d. Geb. d. Röntgenstrahlen **60**:175, 1939.

308. Young, M. D.: Balantidiasis, J. A. M. A. **113**:580 (Aug. 12) 1939.

A detailed analysis of 81 uncomplicated clinical cases of Trichocephalus (whipworm) infection is presented by Swartzwelder.[309] More than two thirds of the patients were in the age group between 6 and 15 years. White patients predominated over Negroes in the ratio of 5 to 1, and there were twice as many females as males. The fact that a diagnosis of chronic appendicitis was made in an appreciable number of instances indicates the importance of infestation with this parasite as a cause of vague abdominal symptoms.

The symptomatology of oxyuriasis is thoroughly discussed by Brady and Wright [310] after careful study of 200 cases. The opinion is expressed that symptoms may be caused by mechanical stimulation and irritation, by allergic reactions or by transportation of the organisms to places where they may become pathogenic. Conscious sensations and enuresis were not common, but evidence is presented that pinworm vaginitis may be much more frequent than it has usually been considered. No abnormal sensations were noted in the majority of cases after the pinworm had migrated onto the skin from the rectal and anal mucosa. In only 1 case of the 200 had appendectomy been performed, and no proof was found that any true relation existed between the occurrence of oxyuriasis and abdominal pain. Moderate eosinophilia was found in over two thirds of the children. Successful treatment was accompanied with an improvement in appetite, weight and color. The same authors [311] present a convincing report on the efficacy of gentian violet in the treatment of pinworm infestation. A total of 224 patients were treated by oral administration of this drug, with exceptionally satisfactory results. A detailed description of the more efficacious methods of treatment, with the contraindications for the use of gentian violet, is given, and the authors seem to be entirely justified in their conclusion that "gentian violet is cheaper and superior to all other methods of treatment." The article offers a valuable contribution to the therapy of this common and frequently intractable and annoying condition. A further contribution is that of Sawitz [312] and her associates, who demonstrate in rather conclusive fashion the superiority of Hall's cellophane-tipped swab method in the

309. Swartzwelder, J. C.: Clinical Trichocephalus Trichiurus Infection, Am. J. Trop. Med. **19**:473, 1939.

310. Brady, F. J., and Wright, W. H.: Studies on Oxyuriasis: The Symptomatology of Oxyuriasis as Based on Physical Examinations and Case Histories on Two Hundred Patients, Am. J. M. Sc. **198**:367, 1939.

311. Wright, W. H., and Brady, F. J.: Efficacy of Gentian Violet in the Treatment of Pinworm Infestation, J. A. M. A. **114**:861 (March 9) 1940.

312. Sawitz, W.; Odom, V. O., and Lincicome, D. R.: Diagnosis of Oxyuriasis: Comparative Efficiency of the N. I. H. Swab Examinations and Stool Examination by Brine and Zinc Sulfate Floatation for Enterobius Vermicularis, Pub. Health Rep. **54**:1148, 1939.

diagnosis of oxyuriasis, which proved to be infinitely superior to the examination of stools by the brine or the zinc sulfate method. Initial swab examinations revealed infection in three fourths of 136 children examined, but at least seven swab examinations were necessary before the absence of pinworm infestation was assured, as subsequent tests by this method revealed an incidence of 96.3 per cent in the same group.

The role of Giardia in the production of gastrointestinal symptoms is still controversial. That the duodenum is frequently the seat of giardial infestation in man is well known, particularly since investigation of duodenal contents has become a routine procedure. An increasing number of reports seem to contain suggestive evidence that human giardiasis is associated with real but rather indefinite disturbances of the digestive tract, which may be relieved by appropriate therapy. The efficacy of atabrine as the most potent parasiticide available for the treatment of giardial infestation is becoming more apparent. A recent report by Morrison and Swalm [313] indicates the value of such therapy as originally outlined by Valerio, and the authors appear to be entirely warranted in their conclusion that: "Despite the absence of control studies, atabrine is definitely helpful clinically in some of the cases." A further article, by Veghelyi,[314] is also of interest in this regard. He has made studies on absorption of fat and excretion of urinary pigment in a group of children infested with Giardia but without evidence of any other disease. In these children absorption of fat was found to be greatly defective, and only a small part of the normal amount of urinary pigment was excreted. Such findings were attributed to the mechanical effect of the parasites on intestinal function. Veghelyi feels that the symptoms commonly attributed to giardiasis in children—anemia and retardation of development—can be adequately explained on the basis of deficient fat absorption. After appropriate therapy, with expulsion of parasites, all symptoms disappeared, the fat absorption and pigment content of the urine became normal, anemia improved and growth commenced.

The high incidence of Trichinella infestation in the United States is well recognized. Examination by Nolan and Bozicevick in 1938 of 1,000 cadavers from different hospitals in Washington and other eastern cities revealed an incidence of 17.4 per cent, and other surveys provide figures ranging from 3.5 to 27 per cent of the local population. It is characteristic, however, of all these findings that very light, nonclinical conditions predominate. A report from North Carolina by Harrell and Johnston,[315] based on examinations of necropsy material, revealed an incidence of

313. Morrison, L. M., and Swalm, W. A.: A New Effective Parasiticide in Giardiasis, Am. J. Digest. Dis. **6**:325, 1939.

314. Veghelyi, P. V.: Giardiasis, Am. J. Dis. Child. **59**:793 (April) 1940.

315. Harrell, G. T., and Johnston, C.: Incidence of Trichinosis in the Middle South, South. M. J. **32**:1091, 1939.

trichinosis in the middle part of the South that appears to be much less than that reported in other sections of the country. The conclusions of these authors are of importance if they are correct. They attribute the lower incidence to the fact that trichinosis, which is a hog-borne disease, is probably caused by meat from garbage-fed hogs. Most southern hogs are grain fed, and the incidence of trichinosis in hogs and in human beings in this particular section of the country appears to be lower than elsewhere. Another fact that may contribute to the paucity of clinical cases of trichinosis as compared with the admittedly large number of infestations in human beings is suggested by the experimental studies of Roth,[316] who was able to establish successful immunity in guinea pigs to reinfections with Trichinella spiralis. This immunity to reinfection appeared to be due to a defense mechanism, which apparently inhibits the maturing and propagation of larvae, but the problem is still unsolved, although it is possible that such immunization may occur in man and may in part account for the infrequency of diagnosable disease.

One point of practical importance in relation to parasitic disease is its frequent association with deficiency disease. Such an association is rather obvious, but the need for general dietary supervision in addition to specific antiparasitic therapy is indicated, for example, in the report by McKenzie,[317] who discusses vitamin B_1 deficiency associated with hookworm anemia. He draws particular attention to the rapid disappearance of edema so frequently noted in cases of hookworm infestation following the addition of vitamin B_1 to the usually accepted forms of treatment.

Regional Enteritis.—Regional enteritis as a disease entity is now generally recognized, and its diagnosis is made with relative frequency, but therapeutic measures still leave much to be desired. Obstructive symptoms due to stenosis or to fistula formation obviously require surgical intervention. It is still not clear whether the ulcerative stage of the disease, characterized by varying degrees of abdominal cramps, diarrhea, the occurrence of anemia and loss of weight is best treated by the surgeon. That a reasonable doubt exists as to the efficacy of surgical intervention under such conditions is expressed to an increasing degree by various authors. Holloway [318] and Rhoads,[319] for example, present a general discussion of the features of this interesting disease, and both recommend conservative treatment in certain of its phases. As Holloway

316. Roth, H.: Experimental Studies on the Course of Trichina Infection of Guinea Pigs: III. Immunity of Guinea Pigs to Reinfection with Trichinella Spiralis, Am. J. Hyg. (Sect. D) **30**:35, 1935.

317. McKenzie, A.: Deficiency of Vitamin B_1 in Hookworm Anemia, Lancet **1**:1143, 1939.

318. Holloway, J. W.: Regional Ileitis, Ohio State M. J. **35**:1059, 1939.

319. Rhoads, J. E.: The Management of Regional Ileitis and Certain Other Ulcerative Lesions of the Intestines, Pennsylvania M. J. **42**:1050, 1939.

expresses it: "There is some difference of opinion, but there is little support for immediate radical resection," as the course to follow when one encounters acute regional enteritis at operation. As Rhoads points out and as is evident from other scattered observations, regional enteritis may occur in an early form with little fibrosis. When gross evidence of fibrosis is not evident, expectant treatment is indicated, "as resolution is frequent." While commenting on the indications and the results of surgical intervention, Rhoads points out an additional aid in the management of obstructive symptoms, namely, decompression by means of the Miller-Abbott tube.

The satisfactory results obtained in a group of cases by Landa and Stritzko [320] following the use of such nonspecific measures as fever therapy with injections of foreign proteins lends weight to the suggestion that medical management of many of these conditions not only is justifiable but may be consistent with excellent results. However, further prolonged clinical observations of this disease are needed before adequate and convincing knowledge is obtained as to the precise therapeutic measures to be employed.

The close association between profound nutritional disturbances and regional enteritis is readily understood. Hypoproteinemia and avitaminosis are fairly well recognized complications, and that such a deficiency may invalidate what might otherwise prove to be successful surgical intervention is pointed out by Casten.[321] He reports 1 such case, in which complete and persistent absence of healing of the abdominal incision was noted during the entire postoperative course, in spite of the fact that no semblance of an infection was present. It seems possible that this failure of wound healing may have been due to vitamin C deficiency. Severe anemia is commonly observed in association with regional enteritis. Plum and Warburg [322] review the literature on a large group of cases and find mention of hyperchromic anemia only once. The authors record observations on 3 additional cases in which the picture was that of severe megalocytic anemia and in 2 of which the patients responded completely to liver therapy. It is of interest to note that in 1 case the blood picture has been completely normal for more than one year without any further treatment with liver. Two patients also showed clinical evidence of pellagra and peripheral neuritis, which responded to vitamin B therapy. The authors make the entirely proper

320. Landa, E., and Stritzko, G.: Fever Therapy in Chronic Enterocolitis, Wien. Arch. f. inn. Med. **33**:145, 1939.

321. Casten, D.: Nutritional Disturbances in Regional Enteritis, Surgery **6**:708, 1939.

322. Plum, P., and Warburg, E.: Hematological Changes, Especially Megalocytic Anemia in Regional Ileitis, Acta med. Scandinav. **102**:449, 1939.

suggestion that some of the regional changes in the ileum itself may represent secondary changes in a vicious cycle.

Ulcerative Colitis.—Continued observations on the etiology of ulcerative colitis fail to reveal any definite specific causative organism and confirm the impressions of Paulson and many others, who consider the disease as a syndrome possibly due to a variable but not yet positively demonstrable cause. Bacteriologic studies by Reed,[323] Dack and his associates [324] and Mintzer [325] serve to illustrate the variety of bacterial invaders considered as possible causes of this serious disease. Additional evidence that indirectly confirms the previously reported work of Lium on the effect of vasospasm in the causation of ulceration of the intestinal mucosa is presented in the experimental results reported by Penner and Bernheim.[326] Conditions of shock were reproduced by continued intraperitoneal injections of epinephrine, with the production of necrotic and ulcerated lesions at different levels in the gastrointestinal tract. That such vasospasm may produce ulceration and at the same time be due to the influence of neurogenic factors is of importance in any consideration of the possible etiologic relation between profound psychogenic disturbances and ulcerative colitis.

A statistical study by Jackman, Bargen and Helmholz [327] on the incidence of ulcerative colitis in children is of value because it indicates the more serious nature of the condition in the earlier decades of life.

The clinical manifestations of this disease have been so frequently described that there is no necessity for reviewing many of the articles that have appeared, which are purely descriptive of the ordinary manifestations to be encountered. Allusion to a single article by Smith and Jackman,[328] however, is warranted, as it calls particular attention to the anorectal complications of the disease. These are frequently encountered and are not only distressing but extremely difficult to treat satisfactorily. Anal abscess or fistula constitutes one of the most common complications

323. Reed, A. C.: Chronic Ulcerative Colitis, California & West. Med. **50**: 402, 1939; **51**:32, 1939.

324. Dack, G. M.; Kirsner, J. B.; Dragstedt, L. R., and Johnson, R.: Agglutinins for Bacterium Necrophorum in Serum of Patients with Chronic Ulcerative Colitis, J. Infect. Dis. **65**:200, 1939.

325. Mintzer, I. J.: Pyoderma Gangraenosum, Onychogryphosis and Onycholysis with Ulcerative Colitis, Arch. Dermat. & Syph. **40**:541 (Oct.) 1939.

326. Penner, A., and Bernheim, A.: Experimental Production of Digestive Tract Ulceration, J. Exper. Med. **70**:453, 1939.

327. Jackman, R. J.; Bargen, J. A., and Helmholz, H. F.: Life Histories of Ninety-Five Children with Chronic Ulcerative Colitis: Statistical Study Based on Comparison with a Whole Group of Eight Hundred and Seventy-One Patients, Am. J. Dis. Child. **59**:459 (March) 1940.

328. Smith, N. D., and Jackman, R. J.: Anorectal Complications of Chronic Ulcerative Colitis, with Several Illustrative Cases, Surgery **7**:69, 1940.

of chronic ulcerative colitis, and in the series of patients reported on by these authors it ranked third, polyposis and stricture occurring more frequently, in the order named. The authors also made one recommendation of great importance, which is so frequently overlooked that it will bear repetition. They stress the obvious necessity for careful proctoscopic examination in cases of rectal bleeding and note that an appreciable number of persons in their series had hemorrhoidectomies during the insidious initial stages of chronic ulcerative colitis. The existence of such a fact is sufficient warrant for the rule obtaining in certain hospitals that a proctoscopic examination must always precede hemorrhoidectomy for rectal bleeding. Such a rule should be applied to general practice, particularly because the performance of hemorrhoidectomy in a patient harboring ulcerative colitis almost invariably lights up the disease and may be responsible for a serious attack.

The results of general bodily depletion associated with ulcerative colitis are fairly well recognized, but several reports are of some interest. Davidson [329] presents observations on 3 patients who had infantilism during the course of the diarrhea incident to serious ulcerative colitis. The potential interference with normal endocrine processes secondary to the deficiency produced by prolonged diarrhea is not generally recognized. Nutritional disturbances, however, are frequently encountered, and it is quite possible that the development of infantilism in these cases in which obviously the patients were in the proper age group—15 to 17 years—was simply another manifestation of nutritional lack, in this case probably some disturbance in the chemistry of the sterones. Clubbing of the fingers is frequently noted, not only with this disease but with regional enteritis and with numerous other chronic nutritional disorders. Schlicke and Bargen [330] presented no new material; however, they emphasize the incidence of this curious manifestation of metabolic deficiency and point out the implication inherent in such a physical finding. Without any question, the finding of clubbed fingers gives a direct indication of the degree of nutritional deficiency that exists as a result of prolonged disease. A most unusual finding is that reported by Rasmussen,[331] who notes the occurrence of multiple areas of calcification in the subcutaneous tissue of a patient with ulcerative colitis. The calcinosis developed at the climax of the colonic disease and disappeared in the course of three or four months, coincidentally with considerable improvement in the colitis.

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329. Davidson, S.: Infantilism in Ulcerative Colitis, Arch. Int. Med. **64**: 1187 (Dec.) 1939.

330. Schlicke, C. P., and Bargen, J. A.: Clubbed Fingers and Ulcerative Colitis, Am. J. Digest. Dis. **7**:17, 1930.

331. Rassmussen, H.: Transient Calcinosis Accompanying Ulcerative Colitis, Acta med. Scandinav. **101**:491, 1939.

As far as treatment is concerned, no new therapeutic measures have recently been evolved. Cheney [332] again reports the efficacy of rather intensive parenteral liver therapy, but his observations lose a great deal of their force when one considers that all of the other usual therapeutic measures, such as dietary supervision, rest and administration of opium, were carried out at the same time, with the occasional addition of a vegetable mucin or of kaolin. That the addition of liver extract to other therapeutic measures may be of real value is not to be doubted; that it has any real effect on the course of the disease, except as a corrective measure for the results of the associated depletion, should be very seriously questioned.

Reports on the use of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′ disulfonate) (oral) and sulfanilamide in the treatment of this disease are of real interest. Brown, Herrell and Bargen [333] present further observations on the continued use of azosulfamide (neoprontosil) and express the opinion that the drug is of definite benefit in helping to control the disease, urging that it be added to the other measures, although recognizing that the clinical response is not predictable and that the drug is in no way curative. Collins [334] similarly reports beneficial results from the use of sulfanilamide, but he, too, points out the necessity of recognizing the natural history of the disease that must be considered in any evaluation of the success attributable to a given form of treatment. It is highly probable that chemotherapy may prove an important addition to measures available in treating this most serious condition. Whatever results are to be expected, however, will probably be due to the effect of such drugs on the secondary bacterial invasion of the colon which invariably accompanies the condition, rather than to any direct effect on the initial causative factor.

The surgical measures to be employed in the treatment of ulcerative colitis are well recognized, as are the indications for their use. The decision that surgical intervention is necessary in individual cases will always constitute a nice clinical point. It is a matter of some surprise that appendicostomy should still be urged as a proper surgical maneuver. The experience of most older surgeons seems definitely to have been that such a measure is followed by disappointing results. It is therefore with some interest that one notes reports by Welcker [335] and Cushman

332. Cheney, G.: Idiopathic Ulcerative Colitis: Effectiveness of Liver Extract in Its Treatment, California & West. Med. **52**:66, 1940.

333. Brown, A. E.; Herrell, W. E., and Bargen, J. A.: Neoprontosil (Oral) in Treatment of Chronic Ulcerative Colitis, Ann. Int. Med. **13**:700, 1939.

334. Collins, E. N.: Chronic Ulcerative Colitis: Sulfanilamide and Other Factors in Its Management, S. Clin. North America **19**:1089, 1939.

335. Welcker, A.: Ulcerative Colitis Considered from the Surgical Point of View, Nederl. tijdschr. v. geneesk. **84**:1400, 1940.

and Kilgore [336] advocating early appendicostomy in this disease. In view of previous disappointing results, it is again proper to suggest that the favorable results attributed to such a move may be merely coincidental and secondary to the cyclic changes to be expected in the chronic forms of this disease.

Lymphogranuloma venereum as a cause of serious rectal disease continues to attract attention. The clinical manifestations are generally well recognized, but the report of David and Loring [337] is of interest, as it records 4 cases of chronic involvement in which squamous cell carcinoma developed in the lesions of the disease. Such an occurrence has been noted previously, but it is of some importance as suggesting the effect of long-standing inflammation in the causation of malignant degeneration. The rather unsatisfactory results of treatment of this disease still constitute a major therapeutic problem. These authors added their experience to that of a few others and expressed the belief that sulfanilamide is of benefit, although in no sense specific in its action. A somewhat similar article is that presented by Hebb and his associates,[338] who record apparently successful results following the use of sulfur compounds, sodium sulfanilate and sodium sulfanilyl sulfanilate. An enthusiastic report on the results of diathermy in the treatment of stricture of the rectum secondary to lymphogranuloma venereum is recorded by Martz and Foote,[339] and results obtained by Martin and de Lorimier [340] after radical therapy are also of interest, although the latter authors are very cautious in alluding to the probable outcome of such measures as applied to rectal lesions. It is evident from the various measures advocated in the treatment of this disease that as yet no specific measures have been evolved, and that carefully controlled studies of the efficacy of the already considered maneuvers are necessary if one is properly to judge their value in attacking such a chronic type of granulomatous disease.

Roentgen Study and Other Diagnostic Procedures.—Although a detailed consideration of the roentgenologic literature is beyond the scope of this review, it is proper to allude to certain articles of particular

336. Cushman, G. F., and Kilgore, A. R.: Appendicostomy for Chronic Ulcerative Colitis, West. J. Surg. **47**:692, 1939.

337. David, V. C., and Loring, M.: Relation of Chronic Inflammation and Especially Lymphogranuloma Inguinale to Development of Squamous Cell Carcinoma of Rectum, Ann. Surg. **109**:837, 1939.

338. Hebb, A.; Sullivan, S. G., and Felton, L. D.: Lymphopathia Venereum Treated with Sulphur Compounds, Pub. Health Rep. **54**:1750, 1939.

339. Martz, H., and Foote, M. N.: Stricture of Rectum Secondary to Lymphogranuloma Venereum: Treatment with Diathermy, J. A. M. A. **114**:1041 (March 23) 1940.

340. Martin, J. I., and de Lorimier, A. A.: Roentgen Therapy in Lymphogranuloma Venereum, Am. J. Roentgenol. **42**:376, 1939.

interest in relation to gastroenterology. Further experience with the roentgen diagnosis of steatorrhea is presented by Kantor,[341] who adds observations on 2 additional cases to those reported in the previous year. He reviews the roentgen findings by which he considers that a diagnosis of this condition may be properly made: changes in the bones, faint filling of the gallbladder revealed by cholecystography, evidences of ileal stasis and colonic dilatation and redundancy, and, as a striking feature, the peculiar smooth appearance of the upper part of the small intestine described as the "moulage sign." In addition to the "moulage sign," he noted in 1 case the occurrence of intermittent dilatation with spasm in the loops of the small bowel, previously described by Mackie, Miller and Rhoads. The importance of the present report lies in the fact that Kantor is able to present the postmortem observations in 1 instance. Necropsy in this case revealed complete loss of intestinal valvulae in the areas where the "moulage sign" had been observed. These observations probably constitute the first report in which a detailed description is given of a postmortem examination confirming the characteristic roentgen findings associated with idiopathic steatorrhea. An excellent description of the condition accompanies the article.

For purposes of reference, the article by Weber[342] on the roentgen manifestations of non-neoplastic lesions of the small intestine is of value. The author described not only the appearance noted in deficiency states, such as sprue, pellagra and celiac disease, but the characteristic findings of chronic enteritis and diverticulosis.

The diagnostic value of roentgenoscopy in cases of acute mechanical ileus is universally recognized, but the article by Chrom[343] is of particular interest, as the author compares the roentgen observations and the operative findings in a group of 32 patients. In 19 of the cases roentgen examination was made within one hour of operation, and in 16 of these the conditions seen at operation agreed entirely with the abnormalities noted by roentgen examination. He points out that it is generally possible to obtain information regarding the location of intestinal distention by means of roentgen examination of the abdomen without the use of a contrast medium, especially in cases of ileus of the small bowel, although such a method cannot be expected to furnish precise information as to the cause, nature and absolute location of the ileus. In cases of obstruction of the large bowel, in which there is no

341. Kantor, J. L.: Further Experience with the Roentgen Diagnosis of Idiopathic Steatorrhea: Report of Cases Including Postmortem Observations in One Case, Arch. Int. Med. **65**:988 (May) 1940.

342. Weber, H. M.: Roentgenologic Manifestations of Non-Neoplastic Lesions of the Small Intestine, J. A. M. A. **113**:1541 (Oct. 21) 1939.

343. Chrom, S. A.: Comparison Between Roentgenologic and Operative Findings in Acute Mechanical Ileus, Acta radiol. **21**:182, 1940.

contraindication to administration of a contrast enema, it is possible to obtain valuable diagnostic aid not only as to the exact level of the obstruction but in many cases as to its nature.

The importance of extra-alimentary causes of abnormalities noted in routine studies of the gastrointestinal tract is fairly well appreciated. Too much importance, however, cannot be attached to the necessity for considering such factors before too didactic an interpretation of the results of roentgen examination as the cause for symptoms referable to the digestive tract has been made. A full summary and discussion of these various factors is to be found in the article by Hubeny,[344] which is worthy of consideration simply as a reminder of the intricacies and dangers attending a diagnosis of gastrointestinal disease. A more provocative article of a somewhat similar nature is that by Oppenheimer,[345] who discusses acute transient intestinal atony on the basis of roentgen examinations. This author describes findings made in a number of patients who on a single examination revealed evidence of an excessive enlargement of the colon, reported as megacolon. For adequate reasons such a diagnosis was not acceptable clinically, and numerous reexaminations of the patients under consideration showed that the colon was perfectly normal in caliber and tone. In 1 case no clinical diagnosis could be made, although intermittent abdominal symptoms were present. In 2 instances a clinical diagnosis of mesenteric thrombosis was made, and in 3 others the presence of renal calculi was demonstrated by roentgen and urologic examinations. It would seem entirely proper to attribute such transient deceptive roentgen findings to reflex disturbances in intestinal motility.

Because of the frequency with which a gastrointestinal aura is noted in epileptic patients, the observations by Robinson [346] are of some interest. One hundred patients with epilepsy were studied by routine roentgen examination of the gastrointestinal tract. Of these, 86 were entirely normal, and in the remainder no uniform abnormalities were noted. It was concluded that the gastrointestinal aura frequently associated with epileptic attacks does not depend on demonstrable gastrointestinal abnormalities.

An interesting roentgen study of perisigmoidal infiltration is that presented by Krogdahl.[347] Starting with a short survey of the occurrence and frequency of colonic diverticula, the author proceeds to

344. Hubeny, M. J.: Extra-Alimentary Causes of Alimentary Filling Defects, Radiology **33**:1, 1939.

345. Oppenheimer, A.: Acute Transient Intestinal Atony, Am. J. Roentgenol. **41**:575, 1939.

346. Robinson, L. J.: Radiologic Gastrointestinal Studies in Epilepsy, Am. J. Psychiat. **95**:1095, 1939.

347. Krogdahl, T.: Roentgenologic Differential Diagnosis of Perisigmoiditic Infiltrates and Sigmoid Cancer, Acta radiol. **20**:241, 1939.

describe the roentgen manifestations of peridiverticula and perisigmoidal infiltration, with especial reference to diagnostic differentiation between these conditions and cancer of the sigmoid flexure. The importance of diagnosis of the latter condition is sufficient to warrant careful consideration of this article.

Technical measures devised for the study of normal physiologic activity of the various portions of the gastrointestinal tract or for diagnosis of pathologic disturbances are always of interest. The value of any procedure, however, must always be subject to careful and prolonged scrutiny. An example of the absolute necessity for a critical evaluation of any new method is shown in the recent reports on the use of orally administered phenolphthalein for the detection of ulcerations in the gastrointestinal tract. Studies carried out by five different groups [348] all indicate the absolute unreliability of this test. A further instance of such unpredictable results incident to the introduction of a new method is indicated in the reports by Hollander, Penner and their associates.[349] These authors described a method for quantitative determinations of phenol red concentration in specimens of stomach contents, in which the dye was used as an indicator of dilution. Application of the method with accurate determinations of the concentration of the indicator gave corrected chloride values that were even greater than three times the isotonic concentration of this ion, a finding which obviously suggested absorption of water from the stomach. Such absorption is unpredictable and tends to introduce an error into the dilution indicator technic which renders it of doubtful value at present.

A relatively new instrumental means of diagnosing gastrointestinal and intra-abdominal disease is peritoneoscopy. The exact clinical value of this method is undoubtedly limited to a very selected group of cases such as are available in large institutions. That such a method is of real diagnostic importance within these limitations is gradually becoming apparent. A review of the results obtained in 100 cases is

348. Suttenfield, F. D.: The Proposed Phenolphthalein Test for Gastrointestinal Disease, M. Ann. District of Columbia **8**:363, 1939. Slutzky, B., and Wilhelmj, C. M.: Phenophthalein as a Test for Gastro-Intestinal Ulceration in the Experimental Animal, Am. J. Digest. Dis. **6**:449, 1939. Notkin, L. J.; Kirsch, E., and Albert, S.: Note on the Value of Woldman's Phenolphthalein Test for Gastro-Intestinal Lesions, ibid. **6**:365, 1939. LeVine, R., and Kirsner, J. B.: An Evaluation of the Phenolphthalein Test of Woldman, Am. J. M. Sc. **198**:389, 1939. Banks, B. M., and Barron, L. E.: Phenolphthalein Test in Gastro-Intestinal Disease, New England J. Med. **221**:296, 1939.

349. Hollander, F.; Penner, A.; Saltzman, M., and Glichstein, J.: Secretory Studies in Whole Stomach: The Determination of Phenol Red in Gastric Contents, Am. J. Digest. Dis. **7**:199, 1940. Penner, F.; Hollander, F., and Post, A.: The Use of Phenol Red as a Dilution Indicator in Gastric Analyses, ibid. **7**:202, 1940.

presented by Benedict,[350] who outlines in detail the indications for use of such instrumentation and the type of information that may be obtained, either by direct visualization or by study of the biopsy material thus obtained. As the dangers inherent in such a method of investigation are almost negligible in the hands of a skilled operator, the more general acceptance of its use in properly selected cases is to be expected. An unusual diagnosis made in this fashion is reported by Ruddock and Hope.[351] These authors, one of whom was the first seriously to advocate the use of peritoneoscopy as a diagnostic procedure, describe their observations in a case of coccidioidal peritonitis. The initial diagnosis, based on peritoneoscopic observation, was probable tuberculous peritonitis, but a final diagnosis of the rare condition coccidioidal peritonitis was made after microscopic examination of the biopsy material.

MISCELLANEOUS CONSIDERATIONS

A variety of relatively unrelated articles have appeared in the gastroenterologic literature during the past year and warrant brief comment. Five separate articles dealing with pain in connection with gastrointestinal or intra-abdominal disease are of diagnostic and physiologic interest. Alvarez[352] comments in an editorial on the clinical observations of de Paula, who subjected over 2,000 patients to Libman's test for sensitiveness. This procedure, of course, has been utilized for some years in an attempt to differentiate the degrees of subjective sensitivity of individual patients. His data on patients with ulcer were more or less in accord with those previously reported by Crohn, who, as one would expect, found that patients with ulcer were more sensitive to the Libman test when hunger pain was present than when they were free from symptoms. De Paula was unable to find any marked difference in the complaints in the two groups of hypersensitive and hyposensitive patients. He found silent duodenal ulcers occasionally in patients who appeared to be hypersensitive, and many of the hyposensitive ones complained of pain. He was impressed with the fact that tender abdominal points appeared more frequently in the hypersensitive group than in the other.

Lewis and Kellgren[353] present observations made in recent experiments related to referred pain, visceromotor reflexes and other asso-

350. Benedict, E. B.: The Value of Peritoneoscopy in Gastroenterology: Review of One Hundred Cases, Am. J. Digest. Dis. **6**:512, 1939.

351. Ruddock, J. C., and Hope, R. B.: Coccidioidal Peritonitis, J. A. M. A. **113**:2054 (Dec.) 1939.

352. Differences in Sensitiveness of Patients with Ulcer, editorial, Am. J. Digest. Dis. **7**:140, 1940.

353. Lewis, T., and Kellgren, J. H.: On the Observations Related to Referred Pain, Viscero-Motor Reflexes and Other Associated Phenomena, Clin. Sc. **4**:47, 1939.

ciated phenomena. Although their results are not entirely in keeping with the observations of others, the conclusions of such careful observers are of interest. The authors believe that there is no special form of pain, referred or otherwise, and no special vasosensory or vasomotor reflex which is the hallmark of visceral disease. Pain of visceral and of somatic origin cannot be distinguished. Deep somatic and certain visceral structures are supplied by a common set of afferent nerves (including pain nerves), stimulation of which produces similar pain and many similar reflex phenomena. This common system, the authors believe, is responsible for all pain and referred phenomena of visceral disease. Variations in reaction depend chiefly on the strength and duration of the stimulus and on the segmental derivation of the afferent fibers stimulated. Kellgren [354] discusses the distribution of pain arising from deep somatic structures, with charts of segmental pain areas. In the observations recorded, segmental areas of deep pain and tenderness have been mapped out by stimulating the interspinous ligaments. An extensive investigation was made of the distribution of pain arising from the various deep somatic structures, and it was found that it presents a gradual transition from pain which is confined to a spot in the region of the structure stimulated to diffuse pain of full segmental distribution. Whether the pain is local or segmental appears to depend more on the depth at which the tissue stimulated lies than on its nature. The authors suggest that the segmental distribution of diffuse pain may be a form of false localization. These studies are of profound physiologic interest and of some practical importance but, as has been noted, are not in close agreement, for example, with many careful clinical observations on so-called somatic pain.

A somewhat different approach to the subject is made by Kinsella,[355] who studied the sensibility of the peritoneal surface. He confirms the work of previous observers as to the sensitivity of the anterior parietal peritoneum but apparently found that, in contrast to the invariable pain response noted on stimulation of the anterior parietal peritoneum, the results of stimulation of the posterior parietal peritoneum of the right iliac fossa varied considerably in different persons. In half of 20 subjects studied in this manner no sensation was found, but in the other half stimulation of the parietal surface caused pain, referred in most cases to the right iliac fossa. The mesentery of the appendix was universally sensitive to physical stimuli, and pain was referred to the midline in most cases. In 14 of 17 patients operated on for acute appendicitis a clinically tender appendix was squeezed at operation and pain was produced. Kinsella reviews previous work

354. Kellgren, J. H.: On the Distribution of Pain Arising from Deep Somatic Structures with Charts of Segmental Pain Areas, Clin. Sc. **4**:35, 1939.

355. Kinsella, V. J.: Sensibility in Abdomen, Brit. J. Surg. **27**:449, 1940.

done on somatic and visceral pain and is in agreement with the idea that a difference exists between the two. He also presents evidence in which he attempts to show that viscera may be directly sensitive to pain and tenderness in the presence of certain pathologic conditions, such as peptic ulcer or appendicitis. The conclusions are in no way novel, but the observations constitute a rather valuable addition to the present knowledge of subjective sensations arising from visceral disturbances.

An article by Brulé and Garban [356] on lumbocrural neuralgias of colonic origin is of interest because of the amplification given to preceding observations of a somewhat similar nature. It has been known for some time, although not sufficiently recognized, that colonic disturbances may cause pain apparently due to conditions involving the spine. The authors bring some apparently satisfactory clinical evidence to indicate that pain due to disease or abnormal disturbances in the colon, such as diverticulitis, may be entirely referred to the lumbosacral area and from there along the distribution of the femorocutaneous or crural nerves. An important point in the discussion is notation of the fact that such pains are extremely transient and may come and go with relative rapidity. The source of their origin is indicated by the fact that they respond much more readily to treatment of the underlying colonic condition than to local measures.

That confusion arises between symptoms due to serious cardiac diseases and those originating in the upper part of the digestive tract is known. The importance of correct differentiation between symptoms of cardiac and of gastrointestinal origin cannot be sufficiently stressed, however, and the difficulties incident to a correct differential diagnosis are frequently so great that they constitute a rather forceful argument against gastroenterology as a strict specialty. Wahlberg [357] reports 3 cases of roentgenoscopically demonstrable esophageal spasm secondary to myocardial insufficiency or coronary disease. In these cases the picture was an inversion of that presented by Jones,[358] Reid [359] and others, who record the occurrence of striking substernal pain with reference down the left arm in younger persons and in those with no electrocardiographic evidences of myocardial involvement. In one of these articles [358] a striking instance is recorded of a patient 30 years of

356. Brulé, M., and Garban, H.: Lumbacrural Neuralgias of Colonic Origin, Presse méd. **47**:1061, 1939.

357. Wahlberg, J.: Esophageal Spasm as Cardiac Symptoms, Acta med. Scandinav. **101**:568, 1939.

358. Jones, C. M.: The Symptomatology of Diaphragmatic Hernia with Some Notes on Therapy, Tr. Am. Clin. & Climatol. A., 1940.

359. Reid, W. D.: Hiatus Hernia Simulating Cardiac Infarction, New England J. Med. **223**:50, 1940.

age who experienced frequent attacks of angina-like pain spreading to the ring and little fingers of the left hand and bearing no direct relation to exercise. Adequate relief was obtained by the use of belladonna and by proper dietary measures, directed toward diminishing the local irritation of a small diaphragmatic hernia. A more complete list of difficulties of the upper part of the gastrointestinal tract leading to apparent cardiac symptoms is outlined by Rodman [360] in an orderly, rather textbook-like discussion of the subject. Confirmation of the intimate correlation between cardiac, esophageal and gastric motor activity is to be found in the clinical and experimental studies of Swalm and Morrison.[361] These authors investigated the behavior of the esophagus and stomach during typical attacks of angina pectoris, and, conversely, attempts were made to demonstrate the occurrence of sudden coronary disturbances associated with acute gaseous distention. Temporary cardiac standstill was observed in 1 patient, apparently following distention of the stomach. In this patient the heart resumed its normal activity immediately on release of the intragastric tension. The authors believe, quite properly, that they have produced evidence of a reflex nature of acute cardiac seizures in attacks of angina pectoris. The fact that 1 patient registered no electrocardiographic changes during anginal paroxyms induced through the digestive tract suggested to the authors that the coronary arteries are not the sole factor involved in the production of anginal pain.

The important influence of abnormal endocrine activity on the digestive tract has been alluded to in an earlier part of this review. Blotner [362] contributes one interesting finding in a study of gastric secretion in patients with diabetes insipidus. In 6 cases the author thought that he found increases in the hydrochloric acid and rennin content of the gastric juice. The interesting observation was made that administration of solution of posterior pituitary apparently caused a definite decrease in these secretions. Gastric roentgen studies revealed no abnormality in 3 of the 6 patients; the fourth had a duodenal ulcer. A less conclusive but rather interesting discussion of the digestive disturbances apparently incident to hypophysial disease is found in a purely clinical article by Morañon and Richet.[363]

360. Rodman, J. S., and Leahman, W. B.: Some Differential Diagnostic Problems in the Borderlands of Gastroenterology and Cardiology, Rev. Gastroenterol. **6**:366, 1939.

361. Morrison, L. M., and Swalm, W. A.: Role of the Gastro-Intestinal Tract in Production of Cardiac Symptoms, J. A. M. A. **114**:217 (Jan. 20) 1940.

362. Blotner, H.: Gastric Analyses and Gastric Symptoms in Diabetes Insipidus, Am. J. Digest. Dis. **7**:73, 1940.

363. Morañon, G.; Richet, C.; Pergola, A., and Le Sueur, G.: Acute Abdominal Syndromes of Hypophysial Origin, Lisboa méd. **16**:589, 1939.

The production of digestive symptoms due to pelvic disturbances is well recognized, but, like symptoms pointing toward cardiac disease, they are at times difficult properly to evaluate. That epigastric distress or other gastric symptoms may divert the attention of the clinician from existing pelvic disease is carefully discussed by Simms and Culley,[364] and a careful perusal of their article will provide further proof of this important clinical fact. These authors cite, for example, instances of vicarious bleeding from the gastric mucous membrane and aggravation of organic lesions of the stomach during catamenia, in addition to the more ordinary symptoms anorexia, nausea and vomiting, which frequently occur in association with disease of the pelvic organs.

That profound calcium disturbances in the body occur as a result of prolonged vomiting is well known, but not so well recognized is the fact that renal calcification may accompany pyloric and high intestinal obstruction. Martz [365] reviewed the history of the literature on this subject, which includes 46 cases of calcification of the kidney secondary to severe and prolonged vomiting, mostly due to cicatricial ulcers of the stomach and duodenum. The chemical changes involved in such a phenomenon are discussed in detail and appear to provide an adequate explanation for such an unusual occurrence in the light of present chemical knowledge. A further example of the relation between disturbances of the digestive tract and alterations in calcium metabolism, as noted in osseous changes, is commented on by Brown and his associates.[366] These investigators studied 50 cases of generalized osteoporosis in adults, in 22 of which there were distinct gastrointestinal symptoms. None of the patients showed the chemical changes in the blood associated with hyperparathyroidism, and the authors attempt to lay the blame for the osteoporotic lesions on physiologic alterations in the gastrointestinal tract. Steatorrhea, chronic diarrhea and hyperthyroidism were not present, and the actual evidence for participation of the digestive tract would seem to be highly problematic. As most of the patients were women in the later decades of life, the instances under discussion would seem to fall more properly under the heading of osteoporosis associated with the endocrine disturbances incident to the menopause and subsequent years, described by Albright and others. However, as a generous proportion of the patients had definite gastrointestinal symptoms, the authors correctly concluded that a further intensive study of the subject from the point of view of the physiology

364. Simms, J. R., Jr., and Culley, J. C.: Gastro-Intestinal Manifestations of Pelvic Inflammatory Disease, South. M. J. **32**:774, 1939.

365. Martz, H.: Renal Calcification Accompanying Pyloric and High Intestinal Obstruction, Arch. Int. Med. **65**:375 (Feb.) 1940.

366. Brown, C. L.; Vogel, R., and Meader, R. P.: Clinical Observations on the Passive Relationship of Digestive Tract Disease to a Type of Osteoporosis, Am. J. Digest. Dis. **6**:628, 1939.

of the alimentary tract is warranted. A more convincing set of observations is provided by a series of articles by Meulengracht [367] on the occurrence of spinal osteomalacia apparently due to dietary deficiency or digestive disturbances. The first report deals with 6 patients with spinal osteomalacia who had obviously been on an inadequate diet for a long period. The second group describes observations on 8 patients who had lived on a somewhat insufficient diet and who had, in addition, gastric achylia. In the third series of patients the diet may have been unbalanced, but these patients are of particular interest because a careful history revealed the continued excessive use of laxatives. The subjective symptoms experienced by these patients consisted in pain in the back and loin associated with demonstrable change in the vertebral column. The author thinks that he is correct in regarding osteomalacia as a result of dietary deficiency, especially an insufficient amount of or an insufficient proportion between calcium, phosphorus and vitamin D. In this connection he cites the work of several investigators who state that the diet of the Danish population is deficient in calcium, phosporus and vitamin D, a rather surprising observation about a people who are well supplied with dairy products and whose general standard of living is commonly thought to be high. The proposed relation between improper calcium, phosphorus and vitamin D absorption and gastric achylia and a consequent improvement of the increased intestinal activity due to the excessive use of laxatives would seem to be entirely reasonable.

Two rare and possibly closely related cases involving a faulty utilization of fat are reported by Reinhart and Wilson [368] and by Tannhauser and Davidson.[369] The first case, recorded by Reinhart and Wilson, is designated as one of intestinal lipodystrophy similar to that first described by Whipple. The early clinical manifestations were predominantly those of a blood dyscrasia, and a tentative diagnosis of pseudoleukemia was made. Subsequent chylous ascites developed, and an obstruction of the thoracic duct due to lymphadenosis was postulated. Fatty diarrhea was not a prominent clinical symptom. Subsequent examination at section revealed a massive deposition of fat in the sinuses of the mesenteric and retroperitoneal lymph nodes, associated with emaciation. The evidence suggests abnormal excretion of fat into the intestinal canal, with increased reabsorption and subsequent deposition into the lymph nodes. The case reported by Tannhauser and Davidson

367. Meulengracht, E.: Spinal Osteomalacia from Deficient Diet or Disease, Acta med. Scandinav. **101**:138, 1939.

368. Reinhart, H. L., and Wilson, S. J.: Malabsorption of Fat: Intestinal Lipodystrophy of Whipple, Am. J. Path. **15**:483, 1939.

369. Tannhauser, S., and Davidson, R.: Gastro-Intestinal Pseudoleukemia: Report of Case, Am. J. Digest. Dis. **7**:45, 1940.

was one of massive fatty diarrhea associated with anemia, emaciation and weakness. In this instance active disease of the liver appeared to be present in view of an increased output of urobilinogen in the urine, a reduction in cholesterol esters, an impairment in galactose tolerance, a reduced albumin-globulin ratio and an increase in plasma fibrinogen. A low level of blood calcium (7 mg. per hundred cubic centimeters) was observed, apparently associated with the fatty diarrhea. Innumerable small nodules were demonstrated throughout the intestinal tract by roentgen examination, suggesting either polyposis or, more probably, gastrointestinal pseudoleukemia.

A much more common type of fat intolerance is that noted in cases of celiac disease, 73 of which were observed by Hardwick.[370] The diagnosis was established by the classic clinical features, diarrhea, anorexia, loss of weight and an excess of normally split fat in the stools in more than one case. The study is of value because of the long time during which the patients were observed. Twenty-two died in the hospital, but all but 10 of the remainder were traced; 17 appeared to have recovered clinically and biochemically for more than three years, and 10 others had been free from symptoms for a somewhat shorter period, a total of more than one third of the entire group. That the absence of clinical symptoms did not imply complete inactivity of the disease was indicated by the fact that 4 patients thought to be well still showed steatorrhea and were considered to be in the quiescent phase of the disease. The author implies that idiopathic steatorrhea of adults represents merely reactivation of celiac disease acquired in early life.

Still another instance of recurrent diarrhea with evidences of hepatic dysfunction, leukopenia and megalocytic anemia is reported by Nordenson.[371] He compares the condition to nontropical sprue, and one is led to speculate as to the possibility that it may be related to the condition in the case reported by Tannhauser, just alluded to. The point of interest is that the case is reported under the subject of atrophy of the spleen.

Minor gastrointestinal symptoms caused by allergic disturbances are common, although recognition of them is not always easy. The appearance of such acute abdominal emergencies as those represented by the attacks noted in patients with Henoch's purpura and angioneurotic edema serve to emphasize the occasional importance of recognizing an allergic mechanism as the major factor in serious upsets of the digestive tract. The mechanism underlying the local production of acute pain or distress under such circumstances has always been considered to be

370. Hardwick, C.: Prognosis in Celiac Disease: Review of Seventy-Three Cases, Arch. Dis. Childhood **14**:279, 1939.

371. Nordenson, N. G.: Atrophy of the Spleen, Nord. med. (Hygiea) **4**:3342, 1939.

partial obstruction due to sharply localized edema, and a moderate number of observations obtained at laparotomy are available to support such a view. Further proof that such a conception is logical was presented by Withers,[372] who attempts to explain the symptom experienced by some allergic patients—difficulty in swallowing—on the basis of an esophageal reaction. Examination of the esophagus by means of the esophagoscope apparently revealed localized edema of the mucous membrane of the esophagus and smooth muscle spasm. The variety of allergens capable of producing symptoms continues to grow in number, particularly with the increased use of various new chemical products. An example of this is contained in the report by Hecht and his associates [373] of a case of generalized facial erythema and abdominal distress characterized by cramps, frequent bowel movements associated with increased mucous secretion and pencil-like stools. Careful study revealed that the case was one of contact dermatitis and gastrointestinal allergy due to tetrabromofluorescein contained in a lipstick used by the patient.

Although the causal relation between lead poisoning and acute abdominal symptoms is well known, the report of Otto and Kuhlmann [374] is of some interest. The authors describe the usual and well recognized manifestations of lead colic, together with the equally well recognized roentgen findings of increased tone and spasm in the small intestine. In addition, however, attention is directed toward a phase of the gastrointestinal manifestations of lead poisoning that is not generally recognized, namely, esophageal disturbances. Abnormal esophageal disturbances, the authors imply, are more frequent than is commonly supposed and consist of symptoms of retrosternal pressure, pyrosis and, in rare cases, regurgitation. Spasmodic contractions and even paralysis of the esophagus have been observed as a result of lead poisoning. Attention is also directed to the existence of inflammatory changes in the wall of the stomach as an associated finding in cases of lead intoxication, with the occasional presence of gastritis and gastric ulcers. It has been pointed out by a few observers that the gastric manifestations of this disease may predominate and that the associated roentgen findings may closely simulate those of carcinoma of the stomach. In this regard the report by Magnuson and Raulston [375] is of interest. Eight cases of

372. Withers, O. F.: Gastro-Intestinal Allergy, with Special Reference to the Esophagus, South. M. J. **32**:838, 1939.

373. Hecht, R.; Rappaport, B. Z., and Bloch, L.: Cheilitis, Fixed Drug Eruption and Gastrointestinal Allergy for Eosin Dye of Lipstick, J. A. M. A. **113**:2410 (Dec. 30) 1939.

374. Otto, H., and Kuhlmann, F.: Behavior of Gastrointestinal Tract in Lead Poisoning: Intestinal Disturbances, Klin. Wchnschr. **18**:1081, 1939.

375. Magnuson, H. J., and Raulston, B. O.: Lead Poisoning in Roofers, J. A. M. A. **114**:1528 (April 20) 1940.

lead poisoning in roofers are reported. The patients had been working as roofers for periods varying from three months to ten years and gave a history of holding the galvanized roofing nails in their mouths while working. None gave a history of any other exposure to lead, and none had had lead colic prior to May 1939, at which time a new type of nail was used. This particular nail was shown to be the source of the lead poisoning, which caused symptoms of colic in all and constipation in the majority of workers. One had neuritis, and a lead line was present in 5 of the 8 cases. In 1 instance there were early signs of hypertension. The blood picture was characteristic. Of particular interest were the diagnoses made on admission of the patients to the hospital, which were correct in only 3 instances, the diagnoses in the other 5 cases being peptic ulcer, cancer of the stomach or appendicitis.

A cause of acute abdominal pain which is unusual, at least to physicians practicing in northern latitudes, is recorded in the report by Daniel [376] of a study of 266 cases of malaria. Nine of the patients in this group had attacks simulating acute abdominal disease, and 6 were admitted to the surgical service for emergency treatment. The abdominal pain was accompanied with nausea and vomiting and in several instances increased steadily in severity. There was definite involuntary spasm of the abdominal wall at the time of admission in 3 patients. The spleen was palpable in only 1 case. Malaria was suspected, and the diagnosis was finally established because of initial leukopenia in 2 cases, a rise in temperature accompanied by leukopenia at some time after admission in 3, the occurrence of an unexplained chill in 2 others and the finding of parasites in routine smears of blood in the remainder. Although malaria occurs with relative infrequency in northern clinics, the increase in travel to malaria-infested countries in recent years makes such a report of interest and importance at present.

An unusual manifestation of myelogenous leukemia is that reported by Jones,[377] who describes a case of this disease from the point of view of the hematologist. The unusual feature was the appearance of extensive ulceration of the small bowel, the ulceration being at the site of myeloid infiltration but affecting all layers of the intestinal wall. One of the ulcers perforated, causing peritonitis.

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376. Daniel, R. A.: Malaria Simulating Acute Surgical Diseases of the Abdomen, Ann. Surg. **111**:436, 1940.

377. Jones, E. E.: Intestinal Ulceration in Myelogenous Leukemia, Lancet **1**:174, 1940.

Correspondence

WIRE LOOP LESIONS

To the Editor:—In an article by Dr. Harry Keil entitled "Dermatomyositis and Systematic Lupus Erythematosus: II. A Comparative Study of the Essential Clinicopathologic Features," in the August issue (ARCH. INT. MED. **66**:339, 1940), the author gives me the credit (in footnote 4, on page 342) for the term "wire loop lesions" used to describe manifestations observed in lupus erythematosus.

Dr. G. Baehr first observed the so-called "wire loop lesions" in the glomeruli in a case of lupus erythematosus in 1921. The autopsy protocols of the Mount Sinai Hospital in that year record the fact that he had already determined that the peculiar material in the capillary walls was not related to amyloid. Shortly after I joined the staff of the Hospital in 1927 as pathologist, he discussed with me his observations of glomerular and widespread vascular lesions in connection with a patient who came to autopsy about that time. When additional clinical and pathologic material became available in 1930, he and I, in collaboration with Dr. Schifrin, restudied all the clinical and pathologic material of the preceding years.

PAUL KLEMPERER, M.D., Pathologist, Mount Sinai Hospital.

Book Reviews

An Introduction to Medical Mycology. By George M. Lewis, M.D., associate and assistant attending dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University; instructor in medicine (dermatology), Cornell University; attending dermatologist to St. Clare's Hospital, visiting dermatologist to Welfare Hospital; and Mary E. Hopper, M.S., assistant in mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. Price $5.50. Pp. 315. Chicago: The Year Book Publishers, Inc., 1939.

The clinical pathologist has received any monograph or book on the subject of medical mycology with hope, at least; the dermatologist, with apprehension. Up to the present the subject certainly has been in a chaotic state, and fundamental research is needed perhaps as urgently in this field as in any field of laboratory diagnosis.

This book does much to simplify the subject, chiefly by giving a series of emphatically positive statements concerning the laboratory diagnosis of mycologic diseases. It places the clinical side of the subject, so far as present information is concerned, within the reach of dermatologists and those general practitioners who desire to do more than prescribe ammoniated mercury and calamine lotion for every affliction of the skin. The first part of the book has a brief historical summary and a few cursory statements concerning classification, structure, physiology and methods of diagnosis. There is an adequate chapter on the trichophytin test, with reports of original observations, and this is followed by a similar, and naturally less comprehensive, chapter on the oidiomycin test. There are some minor discussions of allergic manifestations of immune bodies, and then the real meat of the book begins.

The first of these important sections deals with superficial mycoses, and certainly the illustrations will delight any practitioner of medicine, even if he has passed the dermatologic board. The section on deep mycoses is more superficial, and one finds no reference to Histoplasma or to the clinical manifestations of infections with Alternaria.

The last section of the book deals with laboratory diagnosis, and here there are, again, magnificent illustrations of the gross and microscopic characteristics of various fungi which are commonly encountered. The descriptions which are given of twenty-two fungi are brief and are more dogmatic than would be considered discreet in the light of present knowledge. For instance, the statement in reference to immune reactions in actinomycosis will need considerable amplification for any one to make use of it, especially since no reference is given to the original work on the subject. The basic medium for isolation of fungi is one modified by Weidman from the Sabouraud formula and will be found to be generally useful.

The format of the book is characteristic of what will be called "fine bookmaking." The paper is of the best quality and the type face is extremely legible. However, there is a tremendous amount of waste space in the headings and at the end of chapters; this will not detract from the value of the book except for those whose habit it has been to save.

The material issued to advertise this work makes much of "athlete's foot," but the title is not in the index. However, the subject is discussed in the text under its more scientific name.

There is no question that this book will be favorably received by laboratory workers and clinical practitioners alike and that it will serve as a useful guide to both groups.

La mielosi eritremica acuta (malattia di Guglielmo). By Angelo Baserga. with a preface by Adolfo Ferrata. Pp. 218. Pavia: Tipografia già Cooperativa, 1938.

Hematologists in the United States are familiar with several syndromes in which large numbers of immature red cells are found in the blood and which appear to be definite dyscrasias of the erythropoietic system. Erythroblastosis foetalis and Cooley's erythroblastic anemia are cleancut entities, and the von Jaksch syndrome is less definite. Remarkable outpourings of nucleated erythrocytes and their precursors are observed in the "myeloid reaction" incident to the metastasis of malignant growths to the marrow. This has been called "leukanemia." In Lederer's acute hemolytic anemia and in the hemolytic crises of familial hemolytic icterus many nucleated red cells may be found in the blood films. The Italian hematologists, however, seem to have a corner on a series of disorders described by them as erythremic myeloses. These disorders are classified as intergrades between erythroblastosis foetalis, which they designate as *mielosis eritremica acutissima,* and Cooley's anemia, which is called *mielosis eritremica chronica.* The specific disorder discussed in this monograph is the *mielosis eritremica acute,* or the "disease of Di Guglielmo."

This monograph exhaustively presents some 30 cases of "erythroblastemia" from the Italian literature, in 17 of which the condition is said to be acute erythremic myelosis. The concept that there should be such a disease apparently of a leukemia-like character is not illogical if the proposition is agreed to that erythroblastosis foetalis is a neoplastic, leukemia-like disorder. With this granted it is reasonable to expect various erythroblastic anomalies to coincide with the different types of myeloid leukemia, the severity of which varies with the stage of development of the granulocyte involved. In the pathologic studies of these conditions the different authors have sought the "hiatus leukaemicus" which Naegeli taught defined a leukemia, and have found one with surprising regularity.

The difficulty with the entire subject is that none but Italian hematologists see such conditions. Even Prof. Ferrata, in his preface, states that he has seen none, except that of Di Guglielmo's case, and he does not comment on the accuracy of the diagnosis in that instance. The author of the monograph offers no explanation for the peculiar incidence of the disease. However, a skeptical survey of the case reports is illuminating. Four of the patients had congenital syphilis, and the state of the blood in the majority of the rest is not noted. One patient had a lymphosarcoma; the conditions of 3 sound much like examples of Lederer's anemia, with their brief three to five day courses. On only about half the patients was an autopsy performed, although biopsies of material taken from the bone marrow were made for most of them. Several of the patients were seen but once in pediatric dispensaries, had but one blood count and perhaps a splenic puncture performed, and then disappeared and were not followed up.

One is forced to wonder whether Prof. Ferrata never saw any such conditions because he called them by other—and more correct?—names. Is this perhaps why none have been seen in England and America? Or is there some peculiarity of the Italian bread and soil which produces these dyscrasias? The reviewer believes that Baserga's publication is too shaky a foundation to carry the weight of a new and distinct disease entity.

Roentgen Technique. By Clyde McNeill, M.D. Price, $5. Pp. 315, with 267 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1939.

As is mentioned in the foreword, the book deals chiefly with the ways of exhibiting anatomic structure roentgenographically. This implies, of course, that roentgenographic interpretation must be given due consideration if the technical problem of roentgenography is approached intelligently. Essentially Dr. McNeill's book is a complete atlas of the positions used in roentgenographic procedures. Each procedure is illustrated with a halftone reproduction of a photograph showing the position of the anatomic structure under discussion in respect to the roentgen

tube and the roentgenogram, and in most instances a line drawing of the roentgenogram thus produced is substituted for the roentgenogram. A short description of each procedure accompanies the illustrations.

The book is well constructed in all respects. The index is adequate and the bibliography as extensive as the subject matter demands.

Much interesting and practical material has been collected here. It is probable that Dr. McNeill's book will prove to be of quite as much value to the roentgenologist as it is to his roentgenographer.

Micro-Diffusion Analysis and Volumetric Error. By Edward J. Conway, M.B., D.Sc. Price 25s. Pp. 306, with 49 illustrations. London: Crosby Lockwood & Son, Ltd., 1939.

Ninety pages are devoted to the study of the error in volumetric titration, and can be of interest only to an occasional professional analyst. The apparatus, principles and practice of microdiffusion analysis are discussed for 186 pages; these will be of interest to the biochemist, but the methods will probably not supplant those already in use in the clinical laboratories of this country.

An appendix of 15 pages discusses the measurement of renal function from the standpoint of a general diffusion-pressure equation derived from previously published data and a consideration of the formula for estimation of renal work. This section will interest the physiologist but not the clinician.

Peripheral Vascular Diseases: Diagnosis and Treatment. By William S. Collens, B.S., M.D., and Nathan D. Wilensky, M.D. Price, $4.50. Pp. 243. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher.

This volume is intended by the authors to give ready reference to information concerning the diagnosis and treatment of arterial diseases. There is an excellent chapter on the general principles of therapy of arterial diseases and many details in regard to the management of specific disorders are also given. This portion of the volume is particularly good, for it emphasizes those methods with which the authors have achieved their best results. Intermittent venous compression occupies a very important place and probably rightly so.

The sections on methods of examination and on the general symptomatology of vascular diseases are especially well done, as are the articles on peripheral vascular sclerosis and thromboangiitis obliterans. The writers have obviously had their most extensive experience with these disorders. The section on the diagnosis of vasospastic diseases is the weakest portion of this work.

Die Ischias. By Dr. Hans-Georg Scholtz. Price, 4.87 marks. Pp. 111, with 24 illustrations. Dresden: Theodor Steinkopff, 1939.

This booklet, sixteenth in a series on rheumatic infections edited by Dr. Rudolf Jürgens, is devoted to the subject of sciatica. After a short general discussion on what is understood about the disease, the author deals with the anatomy of the sciatic nerve. The pathogenesis of the disease is considered from many angles, with the conclusion that there is not one etiologic factor, but many. The discussions of symptomatology and diagnosis are followed by a short chapter outlining, in a most practical way, the method of examining a patient whose complaint is sciatic pain. The next chapter, which constitutes over half of the booklet, is allotted to treatment. Great weight is placed on Eppinger's use of aminopyrine in small doses; the author strongly recommends such therapy when the disease is in the acute state. Stress is placed on such measures of physical therapy as baths, heat in all forms and massage. The last two chapters are devoted to prognosis and prophylaxis.

The book is intended, as the author states in the foreword, to aid the German physician in his daily work. It is made as practical as possible and is based on the experience of four years during which the author treated 400 patients ill with sciatica. There are many illustrations. The author's style is an easy one, making for enjoyable reading.

A Textbook of Bacteriology. By Hans Zinsser, M.D., and Stanhope Bayne-Jones, M.D. Eighth edition. Price, $8. Pp. 990, with 116 illustrations. New York: D. Appleton-Century Company, Inc., 1939.

Every reviewer who comments on a book that has gone through many editions always makes the statements that this is another book which has stood the test of time and that a new edition requires little or no discussion. These broad statements may well be applied to the eighth edition of the standard textbook of bacteriology of which Hans Zinsser is the senior author.

The book is packed with information, not only technical in nature but also broad in character, and is most instructive for the public health worker, the internist or, as a matter of fact, any one who is in actual contact with disease.

In the preface to this new edition the authors list the many changes that have been made in the text as a result of the "rapid advances in bacteriology and immunology . . . during the past few years." The section on pathogenic protozoa has been omitted; the authors modestly claim that neither is competent to write on protozoology. A small amount of redundant material has been deleted; some new illustrations have been added. The whole book is smaller in size than the last edition.

This text is too well done to need fulsome praise. Its authors are so competent and so well qualified in their branch of medicine that their opus is without doubt the best book of its kind on the booksellers' shelves.

Maladies de l'intestin. Volume IV. By R. Bensaude, with the collaboration of A. Cain, A. Lambling, J. Rachet, A. Bensaude, F. Bertillon, Massot, and E. Sidi. Price, 90 francs. Pp. 374, with 97 illustrations. Paris: Masson et Cie, 1939.

This is the fourth volume of a series on "Diseases of the Intestine" prepared by R. Bensaude with the aid of many collaborators. This volume includes a discussion of hemorrhoids, anal fissures, pruritus ani, hemorrhoids and angiomas in infants, hemorrhagicopurulent rectocolitis, inflammatory rectal strictures and anorectal actinomycosis. Each subject is presented in the usual fashion, including discussion of etiology, pathology, diagnosis, treatment and the like. All chapters are well illustrated. More than half of the monograph is devoted to a discussion of hemorrhoids.

The material is presented more from a practical medical point of view than from a surgical one. The authors include very little bibliographic data, most of the material being based on their own observations, and they present nothing particularly new. Nevertheless, the simple and practical discussions of their personal experiences, which are based on the clinical methods used in France, probably justify this volume, particularly from an American point of view. This monograph should prove of some value to proctologists and gastroenterologists who, as specialists, are well acquainted with most of its contents. To the French-reading physician in general practice the work should be of very real worth.

Nitrous Oxide-Oxygen Anesthesia. By F. W. Clement. Price, $4. Pp. 274. Philadelphia: Lea & Febiger, 1939.

The great progress that has been made in the past few decades toward perfecting general anesthesia and especially nitrogen monoxide–oxygen anesthesia has been due in great part to the splendid achievements of the late Dr. E. I. McKesson. It is indeed fortunate that the accomplishments, "the teachings and the findings of the 'Master' as well as his own impressions and experiences" are preserved particularly by one who was "his friend, partner and co-worker."

The book is divided into six parts, the first of which considers the theories and signs of nitrogen monoxide–oxygen anesthesia. The second and the third part are concerned primarily with the general and special technics of administration and the advantages and disadvantages of the method. The fourth part deals with its use in the various types of operative procedures. The employment of the

method for dental anesthesia and analgesia is presented in the fifth part, and the physical factors in the administration of gaseous anesthetic agents are discussed in the sixth part.

The book is written in a clear, concise and pleasant style. A summary is presented after each chapter. The seventy illustrations are not only apt and instructive but also well reproduced. The value of the book as a reference would have been considerably enhanced by the inclusion of a bibliography. However, it will serve as an excellent, practical and instructive guide not only to those interested in this specialized field but to all surgeons.

The Neurogenic Bladder. By F. C. McLellan, M.D., Instructor in Surgery, University of Michigan. Price $4. Pp. xvi + 206, with 49 charts, 8 figures and frontispiece. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1939.

This monograph is well worth knowing. It is not long; its bulk is due largely to the appendix and charts. Into one hundred and thirteen pages of solid reading, however, is packed all manner of information, novel to the ordinary clinician, concerning the bladder and its functions.

The author discusses the anatomy, physiology and pathologic physiology of the bladder interestingly and with spirit. He shows that the bladder is a reflex organ, that the bladder reflex, like any other reflex, can be determined and that this reflex is of great importance in neurologic diagnosis; and, finally, he explains how the bladder reflex can best be studied, what cystometry is and how the results of cystometric study are to be interpreted.

There is a bibliography of 118 references at the end of the book, covering the ground from T. R. Elliott's studies of 1907, on the innervation of the bladder and urethra, to the present. The history of the development of knowledge relating to the bladder reflex is of itself worth reading. There is also an adequate index, conveniently arranged for him who wishes quickly to learn anything of the bladder and its anatomy, of cystometry, or of the behavior of the bladder in traumatic myelitis or under a variety of other circumstances. On the whole, the author is to be congratulated. He has put together, attractively, a useful, interesting and informative volume.

Office Gynecology. By J. P. Greenhill, B.S., M.D., F.A.C.S. Price $3. Pp. 397, with illustrations. Chicago: The Year Book Publishers, Inc., 1939.

There has been a marked need for a volume of this type. The majority of general practitioners are not interested in operative gynecology but are intensely interested in office or medical gynecology, which constitutes a large part of their practice. This volume, containing three hundred and ninety-seven pages of clear, concise, interesting subject matter and one hundred and six excellent illustrations, more than meets this demand. Each chapter, whether on cervicitis, vaginitis, sterility or some other gynecologic problem, contains detailed information of practical value. Methods of diagnosis or treatment necessitating hospitalization or expensive equipment are not discussed. Of especial value are the chapters on postpartum care, premarital advice, sterility and contraception. This volume is highly recommended to the general practitioner and should be of inestimable value to him.

Simplified Diabetic Manual. By Abraham Rudy, M.D. Second edition. Price, $2. Pp. 216. New York: M. Barrows & Company, Inc., 1940.

This is a helpful book for the patient, nurse or doctor who seeks up-to-date information on the treatment of diabetes with diet and insulin. The second edition carries an introduction by Frederick M. Allen, who comments on the soundness of the author's method and congratulates him on avoiding fads and reckless extremes of treatment. The dietary part of the book is especially valuable, because of the attention paid to taste and food habits of various nationalities: Italian, Armenian and Jewish. Commendable attention is given to the nutritional adequacy of diets.